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Journal of the Society of Cosmetic Chemists

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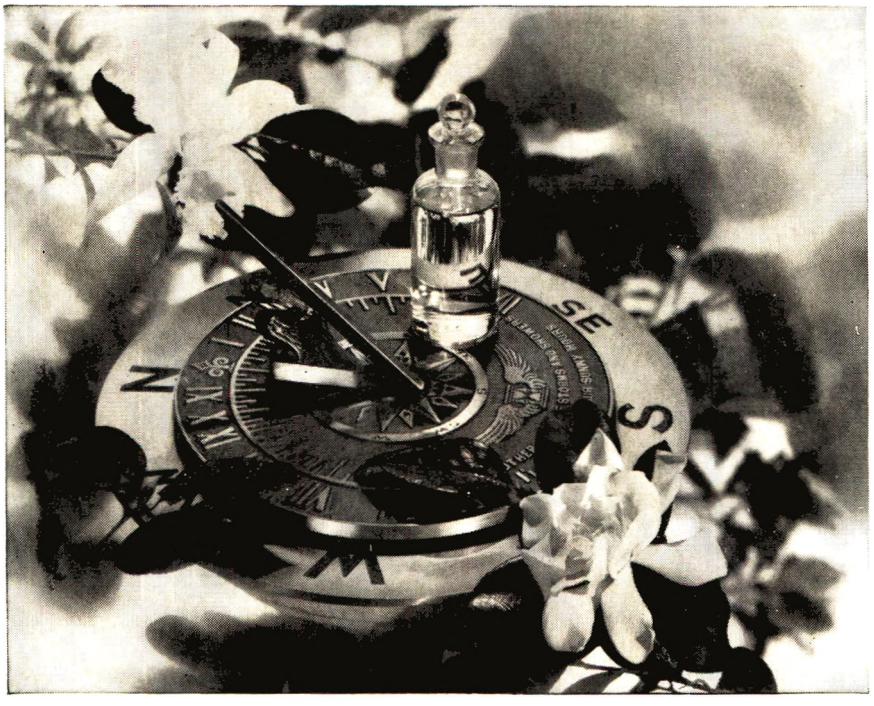

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VOLUME XVI • NUMBER 9

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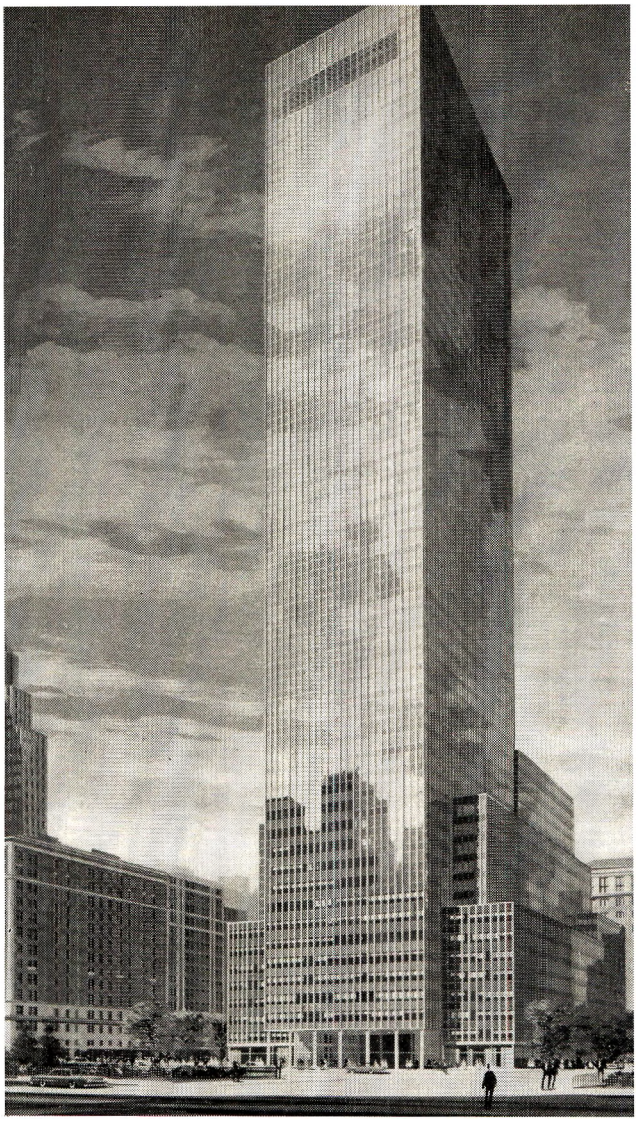

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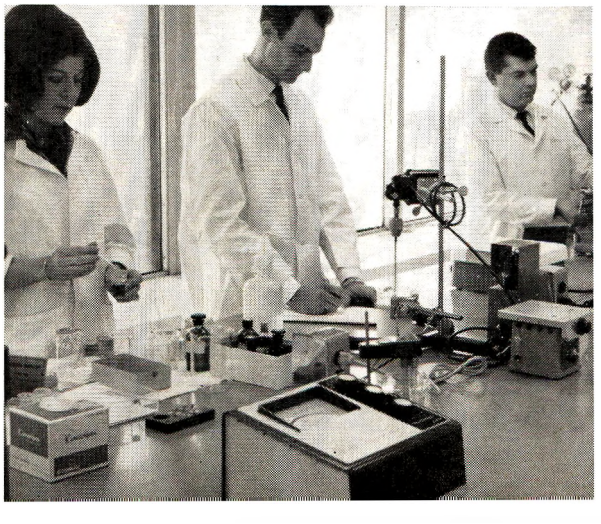

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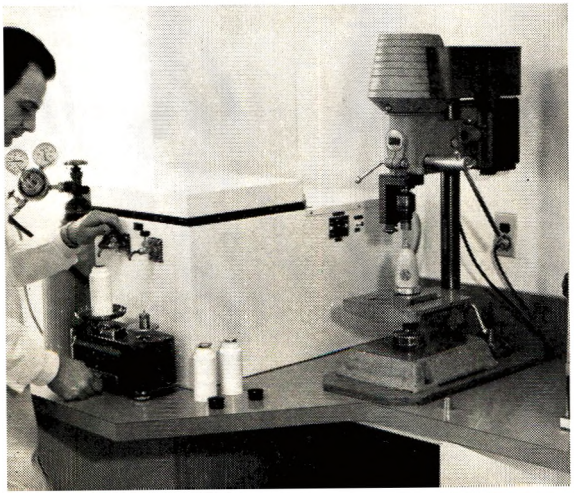

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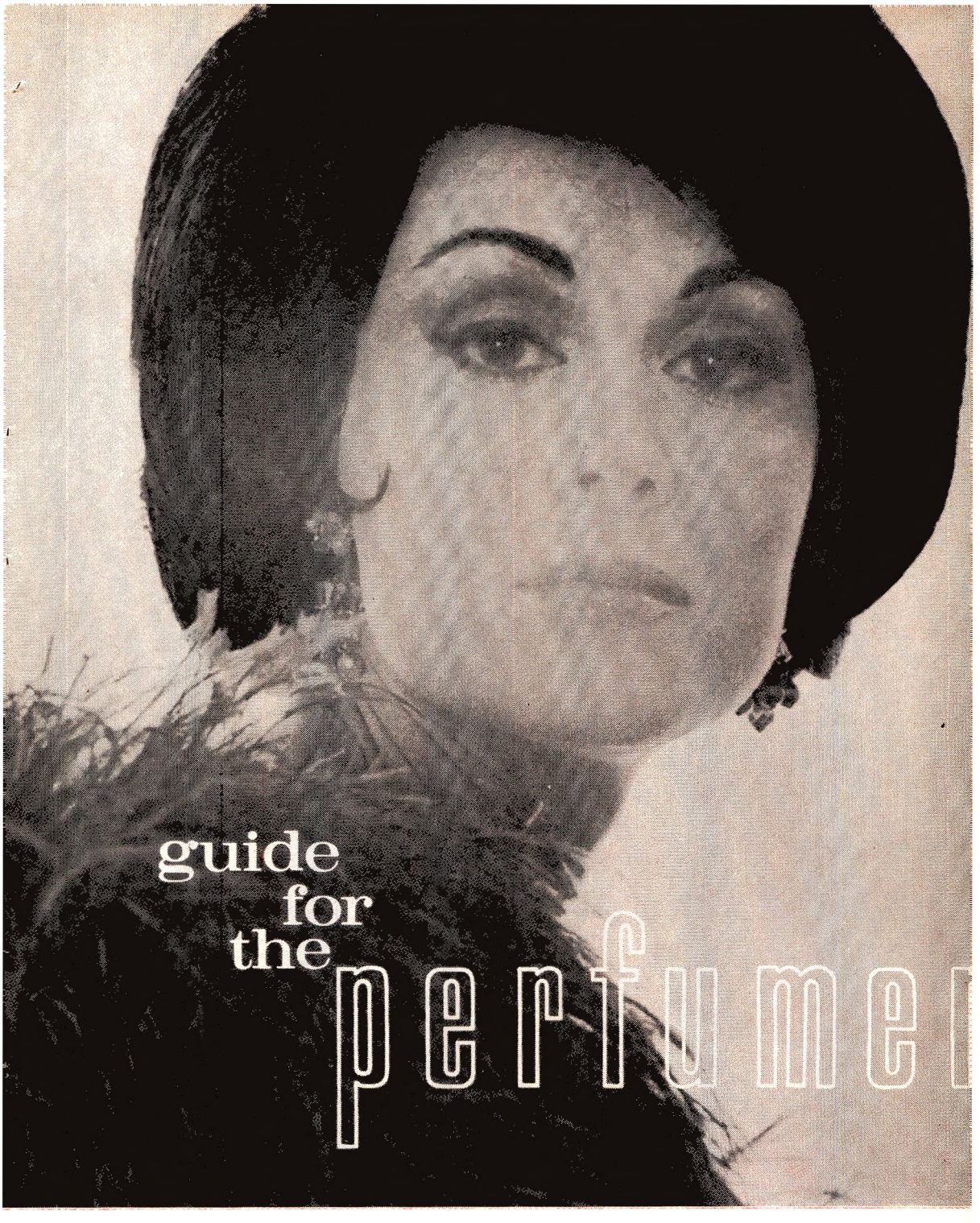

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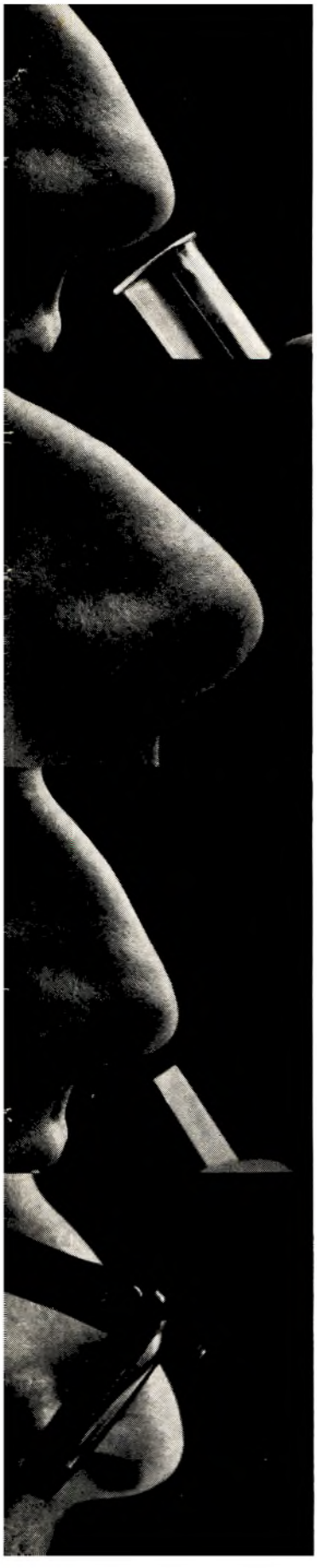

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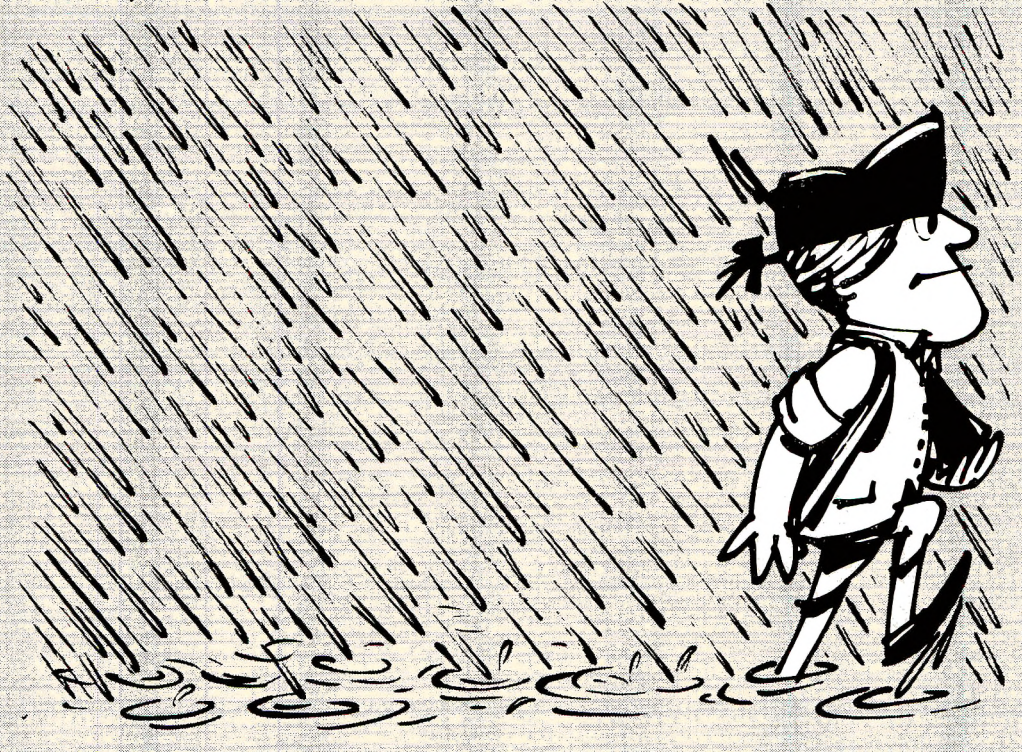

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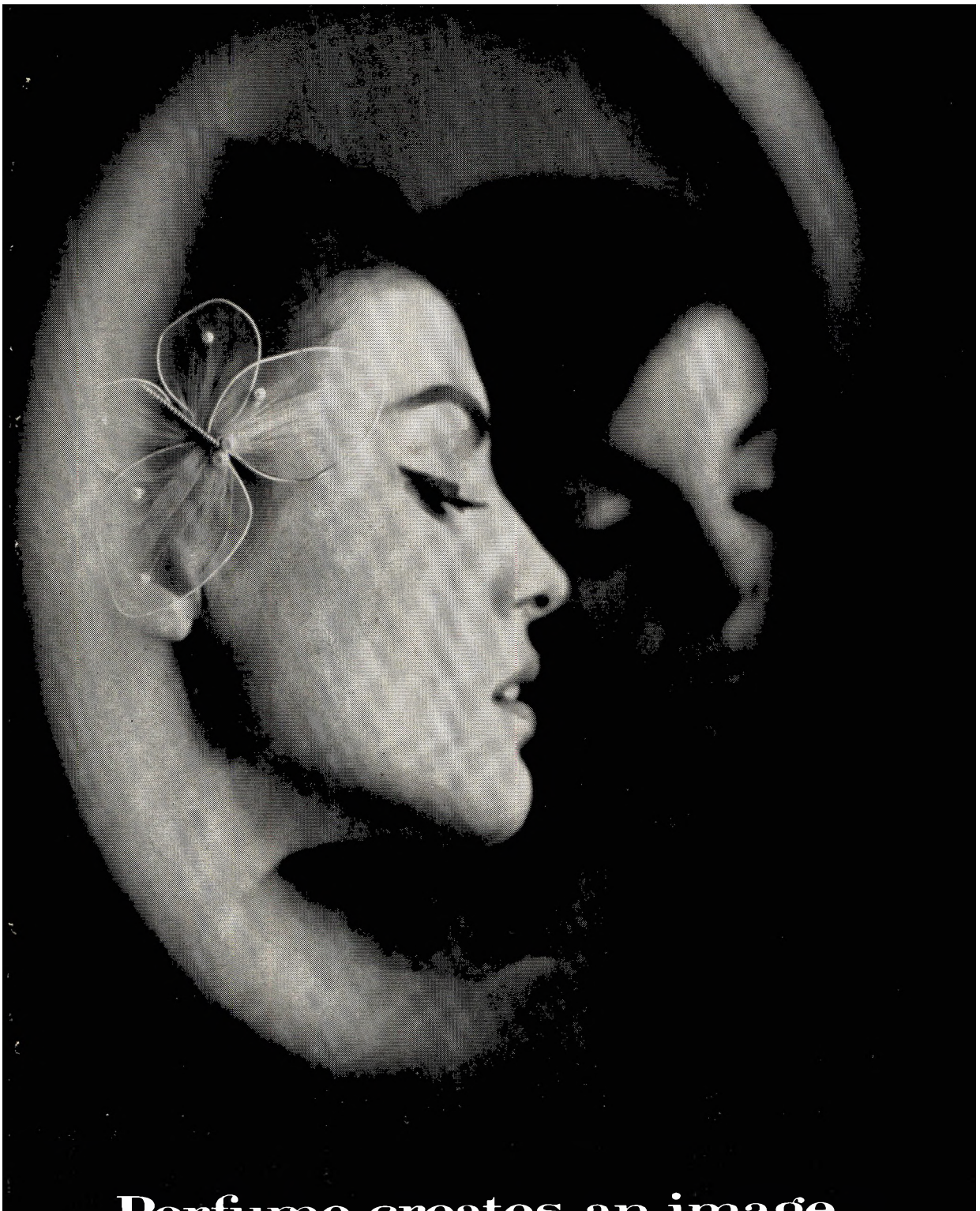

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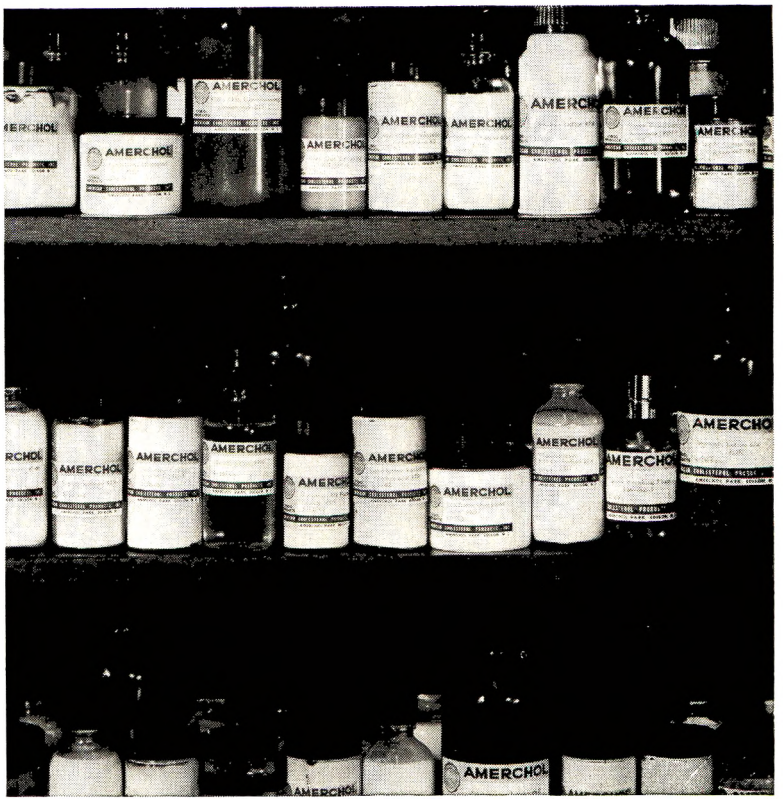

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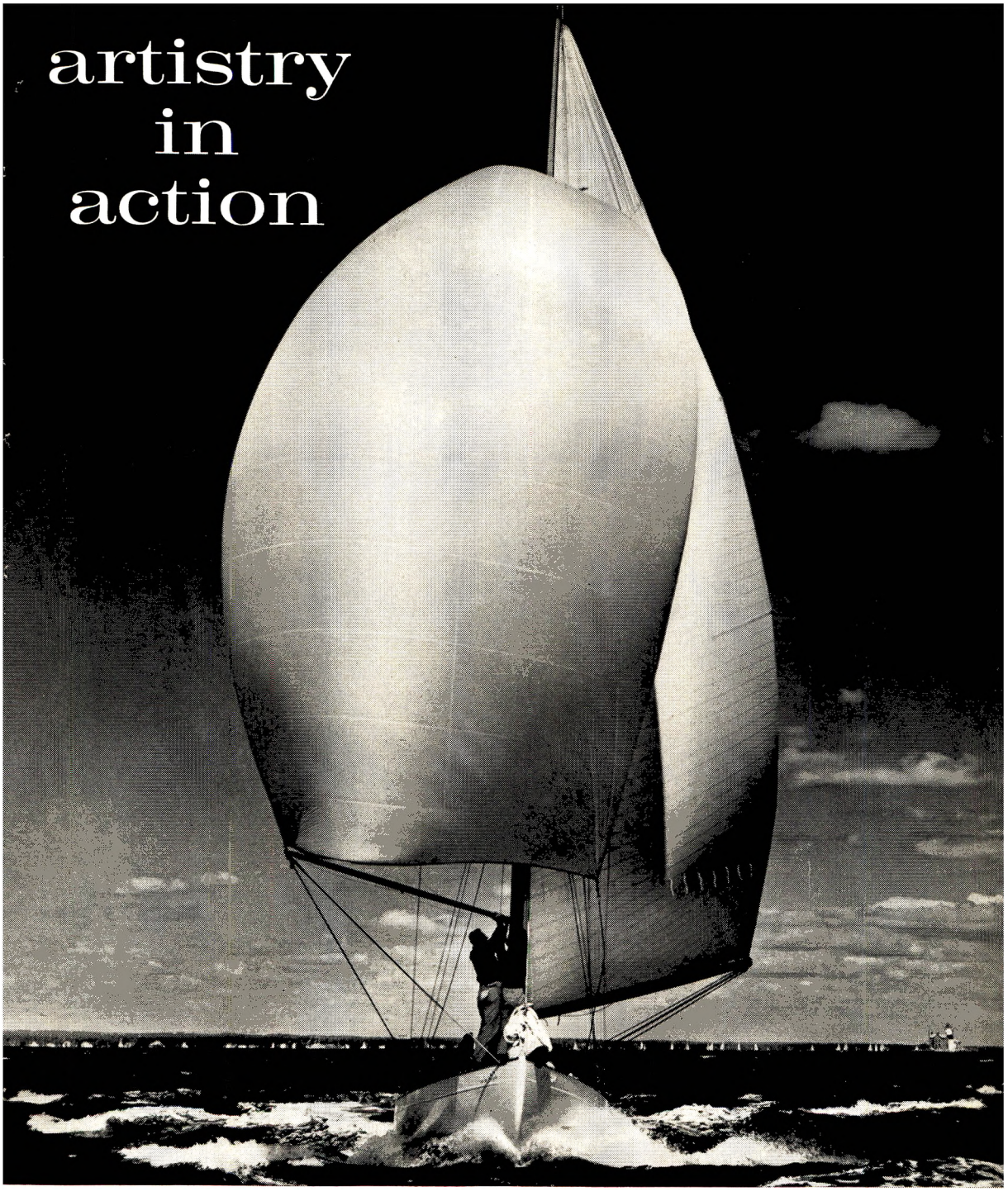

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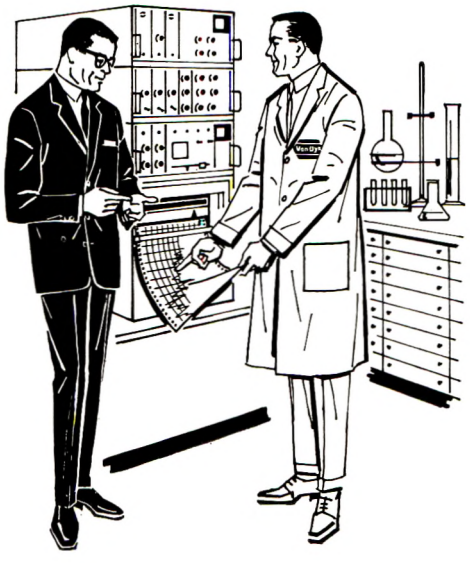

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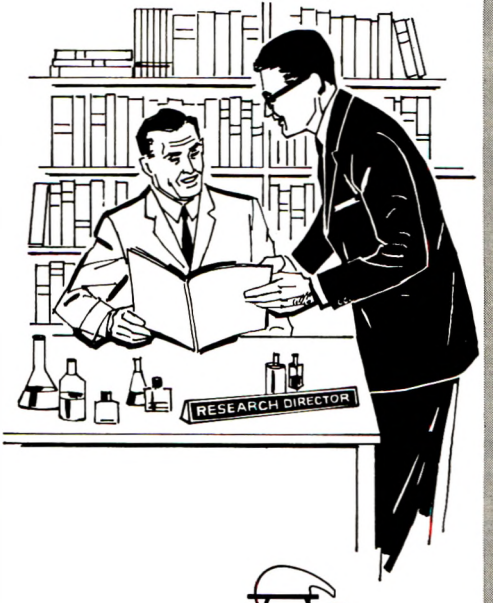

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INDEX TO ADVERTISERS

SYNOPSES FOR CARD INDEXES

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

A comparative chemical study of dandruff flakes, skin scrapings and callus: Karl Laden. *Journal of the Society of Cosmetic Chemists* **16,** 491 (1965)

Synopsis—Comparative chemical analyses of callus, skin scrapings and dandruff flakes have been performed. Compared to normal skin scrapings, dandruff shows lower moisture binding ability, lower ninhydrin-positive material content and higher sulfhydryl and pentose contents. These results suggest that dandruff is associated with an increased rate of keratin formation.

Skin substantivity as a criterion in the evaluation of antimicrobials: Thomas F. McNamara, Marianne L. Steinbach and Benjamin S. Schwartz. *Journal of the Society of Cosmetic Chemists* **16,** 499 (1965)

Synopsis—Skin substantivity is defined as the avidity of a compound for skin tissue. Compounds possessing substantivity were evaluated by two major criteria: (a) qualitatively by measuring the comparative avidity for skin tissue and (b) quantitatively by titrating the release of the compound from tissue. A method was developed to determine each of these properties for compounds having antimicrobial properties. The application of such data to the selection of a compound for a particular topical use was discussed.

The contribution of the resistant cell membranes to the properties of keratinized tissues: E. H. Mercer. *Journal of the Society of Cosmetic Chemists* **16,** 507 (1965)

Synopsis—Electronmicroscopy of hard (hair) and soft (epidermis) keratin suggests that modified cell membranes are cemented by a continuous layer in the former and by a patchy layer in the latter. These differences are related directly to the desquamating nature of epidermis and the persistent behaviour of hair and nails. This intercellular "membrane complex" is more resistant to chemical attack than intracellular keratin but easily dissolved by tryptic or peptic digestion.

Success and failure of odor classification as applied to reactions to erogenous odors: Ernst Paukner. *Journal of the Society of Cosmetic Chemists* **16,** 515 (1965).

Synopsis—One of the problems of successful perfuming is the difficulty of obtaining from consumers an indication of their ideas about the ideal fragrance, appropriate to the product under consideration. An interviewing method is described which reliably defines the consumer's ideal of the desired perfume type. This method (semantic differential) is illustrated with a description of the concept of an "erogenous fragrance."

Several single odorants, at different concentrations, and some well-known perfumes are included in the test. The data are analyzed by factor analysis to determine which of the materials comes closest to meeting the expectation of the ideal. The Henning and Crocker-Henderson methods, traditional systems of odor classification, are evaluated and shown to be less suited for the determination of odor qualities.

Dermal connective tissue alterations with age and chronic sun damage: J. Graham Smith, Jr., and G. Rolland Finlayson. *Journal of the Society of Cosmetic Chemists* **16,** 527 (1965).

Synopsis—The changes in human Caucasian skin commonly believed to be due to aging are primarily the effects of prolonged repeated damage to the skin from the sun. Covered aged skin shows marked differences histochemically and biochemically from exposed aged skin. With aging there is a decrease of nonfibrous protein and of soluble collagen, although the total collagen increases. The total acid mucopolysaccharides decrease, especially hyaluronic acid. In chronically sun damaged skin (actinic elastosis) there is little change in the amount of extractable soluble collagen. The insoluble collagen content is reduced to one-third of that of control skin, and there is an increase in an elastin-like protein. Total acid mucopolysaccharides increase in actinic elastosis, especially hyaluronic acid.

The Eleventh Literature Award

During the luncheon at the Annual Meeting of the Society of Cosmetic Chemists on May 4, 1965, the Eleventh Literature Award was made by the Society President, Dr. Paul W. Jewel, to Drs. William C. Griffin and Paul Becher.

Drs. Griffin and Becher were cited for their many contributions to emulsion technology and, in particular, for their development of a

Society President Dr. P. Jewel (ctr.) presenting Literature Award to Drs. Paul Becher (l.) and W. C. Griffin (r.)

practical procedure for determining the type of emulsifier required. Known as the HLB system, it enjoys widespread use throughout the cosmetic industry and many related industries. It is particularly noteworthy that this is the first time in the history of the Award that it has been presented to working members of the Society and of the consumer industry. Drs. Griffin and Becher were eulogized by Mr. M. G. DeNavarre and presented with an illuminated scroll and an honorarium of $1000.

Extension of Remarks Made by Drs. William C. Griffin and Paul Becher on the Occasion of the Eleventh Literature Award

Dr. Jewel, ladies and gentlemen. We wish to thank you most sincerely and humbly for the honor shown to us.

When notification of the presentation was received from your president, Paul Jewel, he asked that we choose someone for the preliminaries. The choice for us was easy, pleasant, and successful—and we certainly thank Ed deNavarre for his kind words. These thanks must also be extended to a collaborator—you might even say a spy in the ranks, Gardner Harvey, our Atlas Chemmuniqué editor.

Some of us are fortunate enough to have been acquainted with Ed when the Society of Cosmetic Chemists was but a gleam in his eye. Its growth and success are now international. We are all grateful to him for his boundless activity that has resulted in this Society. His idea has truly borne fruit.

The S.C.C. Literature Award provides a desirable incentive for your industry. It is awarded particularly to promote valuable contributions to cosmetic research. The high quality of the cosmetic products that you produce, based on your continued research—for example, the excellent emulsion stabilities that you consistently produce against considerable odds—should be a source of pride for you. If we have had a small part in this effort by serving you, we are grateful.

An occasion such as this is usually devoted to a certain amount of looking backward. However, it may be profitable to take a few minutes to do some looking in the forward direction, even if we're not exactly certain where it is we're going, calling your attention to a few unresolved problems in emulsion theory and technology.

You have sitting before you today two men, the grateful recipients of your Award, who between them have probably spent more time worrying about HLB than anybody else in the world. In fact, it is likely that they have spent over 25 man-years thinking about it. The HLB prin-

ciple, of course, has had an unparalleled success in serving as a guide to the formulation and preparation of emulsions. In spite of all this, and in spite of the aforesaid 25 man-years of effort, we don't know yet exactly what HLB is. However, it seems as though we can stop using the semi-apologetic qualifier "more or less empirical," since there is a growing body of evidence indicating that HLB is a fundamental way of describing a property of surface-active agents.

Here is one instance of this. For years the basic literature has quoted an equation linearly relating the logarithm of the critical micelle concentration for nonionic compounds to the mole ratio of ethylene oxide per molecule of surface-active agent. Unfortunately, this equation is obeyed only over a comparatively small range of values of the ethylene oxide mole ratio. When one attempts to extend this relation over a longer range, significant deviations from linearity occur. However, if instead of plotting the logarithm of the critical micelle concentration against the ethylene oxide mole ratio one plots it against the ethylene oxide weight fraction per molecule, one discovers that the linearity does indeed extend over a considerable range of ethylene oxide contents. Many of you will recognize that the ethylene oxide weight fraction is really only another way of describing HLB; it is, in fact, directly proportional to it in many nonionic surfactants. So, we have the result that the logarithm of the critical micelle concentration is directly proportional to the HLB and not to the infinitely more "scientific" parameter, namely, the ethylene oxide mole ratio.

If we don't know what the HLB value really is, we are in an even worse case when it comes to the matter of the required HLB value for oils and waxes. Not only do we not know what it is, we're not even really very sure how to determine it! Yet certainly, this property of the material to be emulsified is one about which we vitally need information. For the past year we have been toying with the idea that it should be possible to define this property of the emulsified phase in terms of parameters related to the van der Waals-London forces acting between the globules of the emulsified material. If one gives this a moment's thought, it seems like an attractive proposition. However, an accurate computation of this parameter is not easy; but even having done this, we are faced with the fact that there is an extremely high degree of fuzziness in our determination of required HLB, as obtained presently from experimental data.

This leads to another problem area—the question of emulsion stability. Let's not go so far as to worry about how one achieves stability,

although that's a big enough problem, but rather let's just think about how one *defines* stability. Obviously, if one has a completely stable emulsion, there's no problem. And if, on the contrary, one has a completely unstable emulsion, there's no problem, at least of definition. But what do you do about the emulsions in between? Is there any quantitative way in which we can say emulsion A is 1.7 times more stable than emulsion B? As far as we know at the present time, there is no parameter that can be used for this purpose. Yet, a systematic study of emulsion stability requires some such criterion if results are to be meaningfully correlated. Some recently reported results would seem to indicate that in certain systems the shape of a particle distribution curve is maintained during the process of coalescence. If this can be shown to be of wider application, it will then turn out that the only thing we will have to know is particle concentration as a function of time. This sounds almost too easy, and we don't quite believe that it will turn out to be that easy.

Finally, let us turn to a really beautiful problem that especially affects those of us who use nonionic surface-active compounds. For the past several years, some of us working in this field have been off in the corner muttering, "Well, you know, nonionics really are not nonionic." In fact, there seems to be a rather reasonable amount of data indicating the possibility of a small, possibly significant, charge on micelles of nonionics and emulsion particles stabilized by nonionics. In the past year, we have begun to accumulate evidence that these charges are perhaps not so small as we might have believed, although their significance insofar as stabilization of emulsions is concerned is still very much debatable. For that matter, one may comment parenthetically that the precise relation between charge and stability is not at all clearly established even in the case of ionic emulsifying agents. Certainly, however, the nature of this charge, and its relation to HLB, to return fugally to the original theme, remains to be established.

It is remarkable that, in just a few paragraphs, and without really trying, it is so easy to outline enough work for a few lifetimes. We hope that our past contributions have been meaningful and that we will be granted the good fortune to continue to contribute to this fascinating (and exasperating) area of research.

I.F.F. Award 1964

The 1964 I.F.F. Award was presented to Messrs. John Facq, Emil Kirk and Gerbert Rebell by Society President Dr. Paul Jewel on May 4, 1965. Dr. J. Brant acted as eulogist. Mr. Facq is associated with Colgate-Palmolive Co., Mr. Kirk with the Department of Zoology at the University of Chicago, and Mr. Rebell with the Department of Dermatology at the University of Miami.

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

Mr. John Facq (l.) receiving I.F.F. Award from Society President Dr. P. Jewel (ctr.) and eulogist Dr. J. Brant (r.)

CHEMISTS. This award is a means of recognizing the author(s) of the outstanding paper published in an American issue of the JOURNAL during the past calendar year.

The Award for 1964 was made to the authors for their paper, "A Simple Replica Technique for Observation of Human Skin," which appeared in the JOURNAL OF THE SOCIETY OF COSMETIC CHEMISTS on pages 87–98. The I.F.F. Award, which includes an honorarium of $1000, will be made in future years to stimulate original and scientific contributions to the JOURNAL.

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Zawoy, Eugene C., Chesebrough-Pond's, Inc., John St., Clinton, Conn.

Clarification

In the article "The Role of Government in the Field of Cosmetics," which appeared in the Journal, **16,** 85–90 (1965), a reference was made, on page 87, to serious injuries caused by "Koremlu," a depilatory. Immediately following, a reference was made to "Inecto Rapid Notox" and to the effect that the latter product had caused injuries. The author of the paper has advised the *Journal* that it would have been preferable not to have discussed Inecto Rapid Notox in conjunction with Koremlu, since he did not intend to convey the impression that Inecto Rapid Notox contains any inherently dangerous or toxic ingredient. The actual situation that exists with respect to that product is that, as with regard to very many foods, drugs, cosmetics, and other substances, a small percentage of users have adverse allergic reactions.

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A Comparative Chemical Study of Dandruff Flakes, Skin Scrapings and Callus

KARL LADEN, Ph.D.*

Presented before the Chicago Chapter, September 9, 1964, Chicago, Ill.

Synopsis—Comparative chemical analyses of callus, skin scrapings and dandruff flakes have been performed. Compared to normal skin scrapings, dandruff shows lower moisture binding ability, lower ninhydrin-positive material content and higher sulfhydryl and pentose contents. These results suggest that dandruff is associated with an increased rate of keratin formation.

Introduction

In recent years much work has been done in analyzing epidermis and different types of pathological skin scales for various chemical components. Much of this work has been directed toward finding abnormalities in the scales from various pathological skin conditions. In most cases in the literature, results from analysis of pathological scales are compared to results from either callus or epidermis obtained from normal subjects or at post-mortem. In addition, due to different methods of analysis, etc., it is often difficult to intercompare the results obtained by different investigators.

Dandruff (even though it appears in a large percentage of the population) can in some ways be considered a pathological condition. It was

* The Toni Co., Division of The Gillette Co., Chicago, Ill. Present Address: Gillette Medical Research Institute, 6221 N. Capital N.E., Washington, D. C.

TABLE I

Ether Extractables and Water Uptake of Dandruff, Skin Scrapings and Callus

	% Ether Extractables	% H_2O Uptake
Dandruff	39 (30–50)[a]	11 (6–21)
Skin	10 (5–19)	21 (14–39)
Callus	3	16

[a] The figures in parentheses give the range of values obtained for 15 subjects.

therefore decided to study dandruff flakes to see if any chemical abnormalities occur which might help lead to a better understanding of the disease. It was further decided to compare the chemical composition of the dandruff flakes with the composition of skin scrapings obtained from the same subject. It was hoped that the latter might serve as a better control from which to assess abnormalities. Analyses of samples of pooled callus were also included to facilitate comparison with literature values.

Materials

Dandruff was collected from 15 male subjects by brushing the hair one week after the hair was washed with a mild shampoo. During the period in which the dandruff was collected, the subjects did not apply any preparations to their hair.

Skin scrapings were obtained by gently scraping the back of the hand with a dull razor blade. Using care, almost pure stratum corneum can be obtained in this manner. Before sampling, the hands were washed and thoroughly dried, and the hairs on the back of the hands were removed with a hair clipper.

Both dandruff scales and skin scrapings were stored in capped vials in a desiccator at 4°C until analyzed. They were used directly for this study without any further treatment (such as grinding). All samples were collected during the months of May and June.

Callus was obtained from a chiropodist who did not use any topical treatment on the callus before cutting it off. The callus was ground with dry ice, and the fraction which passes through a 125 mesh and was retained by a 200 mesh sieve was used for this study. The powdered callus was also stored in a desiccator.

Experimental and Results

The first point for determination was the lipid content of the samples. Weighed samples of keratin were extracted with three 3 ml. portions of

ether, allowing one-half hour for each extraction period. The ether was removed from the samples using a capillary syringe and the amount of ether extractables present in each sample calculated. The results are presented in Table I.

As can be seen in Table I, the lipid content of dandruff flakes was, as expected, considerably higher than that of skin or callus. This mainly arises from the fact that the lipid accumulates on the scalp while it is constantly washed off the hands. Also, the concentration of sebaceous glands is considerably higher on the scalp than on the back of the hands.

The ether extracted flakes were next thoroughly dried and then allowed to equilibrate in a constant relative humidity chamber at 81% RH. The water uptake for each sample was then calculated. The data obtained are included in Table I.

While these data present averages which only suggest a lower water binding capacity for dandruff flakes *vs.* skin scrapings, a look at the individual data for every subject shows that, in all 15 subjects tested, the

TABLE II

Ninhydrin-Positives as Per Cent Isoleucine in Dandruff, Skin Scrapings, and Callus

Subject	Ninhydrin-Positives (As Per Cent Isoleucine)		
	Dandruff	Skin	Δ
1	5.8	18.3	−12.5
2	13.3	19.0	− 5.7
3	11.2	19.6	− 8.4
4	6.7	22.0	−15.3
5	6.5	23.5	−17.0
Callus	...	10.4	...

water-binding capacity of their dandruff flakes was lower than that of their skin scrapings; this suggests that there is a real lowering of the water-binding capacity of dandruff keratin *vs.* skin keratin.

Since it was known that an important part of the water-binding capacity of skin resides in its water-soluble nitrogenous components, it was next decided to investigate this fraction.

To about 5 mg. of a fat-free sample in a vial, 3 ml. of water was added. The vial was then capped and placed on a mechanical shaker for twenty hours. After centrifugation, an aliquot of the clear supernatant was taken for analysis. The ninhydrin-positive material content of this aliquot was then determined, following the procedure of Rosen (1). A calibra-

tion curve was made using isoleucine as a standard, and the results were expressed as ninhydrin-positives in terms of per cent isoleucine. The results are presented in Table II.

Again, a difference is seen between dandruff and skin, the skin having more water-soluble ninhydrin-positive material than dandruff. This is true in spite of the fact that the hands are usually washed frequently, allowing for extraction of water soluble materials. This higher content of nitrogenous extractables may explain the higher water-binding ability seen in skin scrapings.

Sulfhydryl levels in the keratin were determined by a modification of the procedure described by Flesch and Khun (2). One mg. of finely pulverized Bennett's reagent dye was dissolved in 100 ml. of amyl acetate. One ml. of water and 2 ml. of Bennett's reagent were added to a vial which contained about 5 mg. of defatted keratin sample, and the vial was capped and shaken overnight. After centrifugation, 1 ml. aliquot of the Bennett's reagent was transferred to a test tube, and 0.5 ml. of concentrated HCl was added. After mixing and allowing to stand one hour the O.D. was read at 540 mμ. Glutathione was used to prepare the standard curve. The results are presented in Table III.

As can be seen, the sulfhydryl level of dandruff of each of the five subjects tested was higher than that of their skin.

Lastly, the water-soluble pentose levels were measured. Defatted keratin samples were extracted with water in a manner analogous to that used in extraction of ninhydrin-positive material. The aqueous extracts were concentrated to smaller volumes under reduced pressure, and the pentose content was determined by the orcinol method described by McRay and Slattery (3).*

Standard curves were prepared using ribose. The results are presented in Table IV.

Here again differences exist between skin and dandruff as determined by increased orcinol-reactive material in the dandruff scales. Attempts were made to chromatograph these extracts and to stain for sugars to see if any qualitative differences occurred; however, no pentoses or hexoses were detected in the chromatograms of the extracts of dandruff, skin or callus. A similar failure to detect free sugars via chromatography of the extracts of psoriatic scales has been reported by Wheatley

* In a recent paper by Berry and Warkany (5), it has been suggested that the water extractable material from skin responsible for the positive reactions with orcinol may not be pentose but a bound organic phosphate such as uridine diphosphoglucose. Such materials when reacted with orcinol give colors similar to that obtained with pentoses. In this paper, however, orcinol positive material will be considered as pentose.

TABLE III

Sulfhydryl Levels of Dandruff, Skin Scrapings and Callus

Subject	Sulfhydryl Concentration (mM × 10^{-2} per 100 g.)		
	Dandruff	Skin	Δ
6	41.8	30.6	+11.2
7	44.5	7.9	+36.6
8	20.0	7.0	+13.0
9	53.3	14.5	+38.8
10	20.9	20.0	+0.9
Callus	...	21.2	...

TABLE IV

Pentose Content of Dandruff, Skin Scrapings and Callus

Subject	Pentose Content (mg./100 g.)		
	Dandruff	Skin	Δ
11	242	96	+146
13	210	126	+84
14	261	92	+169
15	451	312	+139
Callus	...	129	...

and Farber (4). These authors concluded that the extracts contain interfering substances which, by forming some type of combination product, prevent the detection of ribose chromatographically.

Finally, chromatograms were run on aqueous extracts of skin and dandruff and sprayed with a xylose-aniline reagent (6). This reagent locates acids of the citric acid cycle (or Krebs Cycle) and various related organic acids. Both qualitative and quantitative differences appeared, suggesting a higher concentration of these acids in dandruff scales as compared to skin scrapings.

Discussion and Conclusions

In the course of these studies several differences have been uncovered between the chemical composition of skin scrapings and dandruff flakes. Of particular interest in this study is that analyses of dandruff flakes have been compared to skin scrapings obtained from the same subject.

Thus far, all of the abnormalities seen in dandruff flakes resemble those seen in other types of exfoliative dermatitis, especially psoriasis (which has been most investigated). Therefore, a closer examination of the causes for abnormalities in psoriatic lesions may also explain the results obtained with dandruff.

It seems clear that in psoriatic skin the rate of epidermal prolifer-

ation is greatly increased. Thus Rothberg, Crounse and Lee (7) have demonstrated that radioactive amino acids administered intravenously appear in normal stratum corneum in about 27 days, indicating that normal skin has a turnover time of about 27 days. In psoriatic skin, it took only three to four days for the C^{14}-amino acid to appear in radio labeled protein in the psoriatic skin.

Recently, Van Scott and Ekel (8) measured the mitotic level in normal skin and psoriatic skin. Their evidence suggested that in psoriasis there is increased epidermal proliferation (or epidermal hyperplasia) brought about by an expansion of the germinative cell population rather than by an increase in mitotic activity of a fixed population of germinative cells. Using their data they calculated the approximate replacement time for normal and psoriatic skin and obtained values approximately the same as those found by Rothberg.

This hyperplasia of the epidermis can serve to explain most of the chemical abnormalities seen in psoriatic as well as dandruff flakes. It has been reported (9) that the sulfhydryl content of successive layers of human skin increases with increasing depth. In hyperplasia, the increased keratin turnover results in the deeper layers of the skin emerging to the surface more rapidly. This would be expected to result in incomplete crosslinking and therefore a higher sulfhydryl content in the upper layers. This higher sulfhydryl content has been reported for psoriatic scales by many investigators (9–11). The increase in sulfhydryl levels seen in dandruff flakes is considerably lower than that found in psoriatic scales. The data presented, however, clearly suggest an increased level as compared to normal skin.

Similarly, it is believed that during the keratinization process the catabolism of some of the cellular proteins results in the accumulation of free amino acids in the stratum corneum (12, 13). Again, the increased keratin turnover in hyperplasia could easily result in a deficiency in the free amino acid content of the skin and a reduction in ninhydrin-positives content. Such a change might also explain the decreased water-binding capacity of the scales. This type of decrease in moisture binding and free amino nitrogen in aqueous extracts has been found in psoriatic scales (12).

Lastly, the increased pentose content seen in hyperplastic scales (4, 14) would also be expected from too rapid keratin turnover. During keratinization, the nuclear and cytoplasmic material from epidermal cells is broken down and metabolized. In psoriasis, the nuclear material is often not completely catabolized, as evidenced by the presence of occasional nucleated cells in psoriatic flakes. This incomplete break-

down would result in a high content of pentose (or perhaps it might be best to say, high content of orcinol-positive material).

The concentration of "pentoses" in the aqueous extract of dandruff flakes was found to be considerably higher than that found in skin scrapings. The pentose content of dandruff flakes has been previously reported by Bolliger and Gross (13), and the values reported herein are in general agreement with their data.

Further evidence for this type of incomplete metabolism of cellular material is seen in the higher amounts of citric acid cycle organic acids which appear in the chromatogram of dandruff *vs.* normal skin.

Thus, the evidence collected here suggests that dandruff is a form of epidermal hyperplasia involving an increase in epidermal turnover. Whether this increase is due to increased mitotic index or an expansion of the germinative layer is unknown. The evidence collected does not support the contention that dandruff is merely normal flaking which adheres to the scalp because of large amounts of sebum, or being held by the hair. In addition, the theory relating dandruff to incomplete breakdown of the cementing substances, if true, probably is also based on too rapid an epidermal turnover.

Finally, while this study points up the nature of the scaling phenomena in dandruff, it unfortunately sheds no new light on the causative factor.

Acknowledgments

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The Fourth Congress of the I. F. S. C. C. will take place in Paris in June, 1966.

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Skin Substantivity as a Criterion in the Evaluation of Antimicrobials

THOMAS F. McNAMARA, Ph.D., MARIANNE L. STEINBACH, B.S., and BENJAMIN S. SCHWARTZ, M.S.*

Presented before the New York Chapter, September 9, 1964, New York City

Synopsis—Skin substantivity is defined as the avidity of a compound for skin tissue. Compounds possessing substantivity were evaluated by two major criteria: (a) qualitatively by measuring the comparative avidity for skin tissue and (b) quantitatively by titrating the release of the compound from tissue. A method was developed to determine each of these properties for compounds having antimicrobial properties. The application of such data to the selection of a compound for a particular topical use was discussed.

Introduction

The trend toward the topical application of antimicrobial substances in cosmetic preparations and proprietary formulations has been increasing for several years. This is evidenced by the fact that the number and types of medicated cosmetics are now approaching in number those of the nonmedicated ones. A large number of chemical compounds with similar antimicrobial, physical and chemical properties and toxicity levels are available for use in topical formulations. If one is to choose the best compound for topical application, an additional criterion must be established. Such a criterion for evaluating these compounds is their avidity for tissue and their elution from it in an active form (tissue substantivity).

This report is concerned with the methodology used in the *in vitro* evaluation of four antimicrobial agents with regard to their tissue substantivity.

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

Materials and Methods

Agents: For use in these studies, samples of 4-amino-1-laurylquinaldinium acetate monohydrate (Laurodin acetate),* 1,1′-hexamethylene-bis[5-(2-ethylhexyl)biguanide] dihydrochloride (Sterwin #904),† alkyldimethylbenzylammonium saccharinate (Holichem HQ 3300),‡ and the 1-hexadecylpyridinium chloride (C.P.C.)§ were obtained from commercial sources.

For the microbiological studies, solutions were prepared in the following manner. Aqueous or aqueous-alcoholic stock solutions of the compounds were prepared at concentrations of 1000 μ/ml. and stored in the refrigerator until used.

In Vitro Tests: The organisms tested were obtained either from the American Type Culture Collection (AATCC) or from our own stock culture collection (WLRI).

Three basic media were used in these studies, brain heart infusion broth (Difco) for the bacteria, Sabouraud's dextrose broth (Difco) for *C. albicans*, and AATCC broth (Difco) for the determination of bactericidal activity of the compounds. (Exception: *F. polymorphum* was cultured in a mixture (1:1) of brain heart infusion broth (Difco) and fluid thioglycollate (Difco)). The determination of the minimum inhibitory concentration for each of the organisms was carried out by the twofold broth dilution method. The inoculum used, except for *F. polymorphum*, was 0.1 ml. of a 1:1000 dilution of a 50% transmission (Lumetron Colorimeter Model 402E equipped with M 465 filter) of a twenty-four-hour broth culture. For *F. polymorphum*, the inoculum used was 0.1 ml. of a 50% transmission of a twenty-four-hour broth culture. All cultures were incubated at 37°C for forty-eight hours. The minimum inhibitory concentration was recorded as the lowest concentration of the compound at which there was no visible growth of the organism.

The bactericidal activity was determined for each compound according to the U.S.F.D.A. (1) method for testing antiseptics and disinfectants. In those cases where a neutralizer was available to obviate possible bacteriostasis of the test substances, the appropriate neutralizer was added to the subculture medium. These neutralizing substances were: 0.05% sodium thioglycollate for mercurials and other

* Allen & Hanburys Ltd.
† Sterwin Chemicals, Inc.
‡ Hollichem Corp.
§ K & K Laboratories, Inc.

heavy metals or for oxidizing agents, letheen (0.07% azolectin and 0.5% Tween 80*) for quaternary ammonium compounds, and 1% Tween 80 for bis-phenols.

Skin substantivity studies were carried out using calf skin discs prepared from calf-skin (dehaired, untanned, and pickled) obtained from Barrett & Co., Newark, N. J. The method of preparation was a modification of that of Vinson *et al.* (2). The calf skin was immersed in a salt solution containing 31.2 g. of sodium chloride and 2.5 g. of sodium bicarbonate per 1000 ml. of distilled water. The ratio of calf skin to salt solution was 1:4 (w/v). When the calf skin reached a pH of 5.6, as ascertained by measuring pH of liquid squeezed from the skin, it was rinsed thoroughly in water to remove excess salt. It was then dehydrated by passing through two daily changes of 95% ethanol. The dehydrated skin was pinned to a board and allowed to air dry (five to six hours). Discs were cut from the dried skin using a 15 mm. diameter cork borer and discs weighing 70 mg. (±20 mg.) were sterilized by ethylene oxide prior to use in tissue substantivity determinations.

Results

Determination of Minimum Inhibitory Concentration. The inhibitory concentrations of the four test compounds for each of the test organisms is presented in Table I. Repeated tests using the same strains on rare occasions showed slight but insignificant variations in these reported concentrations. Each of the compounds was more effective against the gram-positive organisms than it was against the gram-negative organisms and all of the compounds were equally effective against the yeast, *C. albicans*. The addition of protein, in the form of horse serum, reduced the antimicrobial activity of each of the compounds. While all of the compounds displayed excellent antimicrobial properties, none of the four evaluated compounds possessed significantly greater activity against all of the test organisms (see Table I).

Bactericidal Activity. The results of the evaluations of each of the compounds for bactericidal activity against *S. aureus*-209 are presented in Table II. Each of the compounds is bactericidal at the lowest level tested. The differences in killing times vary slightly from compound to compound but these differences are not significant. Furthermore, in routine use, the minimum concentration in a topical preparation would not be less than 1000 γ/ml. and for this reason no one of the com-

* Atlas Chemical Industries, Inc., Wilmington, Del.

TABLE I

Minimum Inhibitory Concentration Against Selected Microörganisms
(γ/ml.)

Organism and Strain #	Hollichem Hq 3300		Sterwin #904		Laurodin Acetate		C.P.C.	
	BHI[a]	BHI & HS[b]	BHI	BHI & HS	BHI	BHI & HS	BHI	BHI & HS
S. aureus WLRI 296	0.4	0.9	0.2	0.9	0.9	3.9	<0.2	...
L. buccalis WLRI 297	<0.2	1.9	<0.2	1.9	0.2	7.8	0.2	...
Str. mitis WLRI 298	0.4	7.8	<0.2	1.9	0.2	15.6	...	...
Str. faecalis WLRI 299	...	...	...	...	...	...	0.2	...
K. pneumoniae WLRI 300	>50.0	>100.0	...	>100.0	50.0	>100.0	31.2	...
L. acidophilus WLRI 301	3.9	15.6	0.9	3.9	3.9	15.6	3.9	...
F. polymorphum ATCC 10953	31.2	...	31.2	...	31.2	...	31.2	...
C. albicans WLRI 045	1.9	>31.2	0.2	>31.2	1.9	>31.2	1.9	...

[a] Brain heart infusion broth (Difco).

[b] Brain heart infusion broth (Difco) with horse serum added.

TABLE II

Bactericidal Activity of the Four Test Compounds Against *S. aureus*-209

Compound (γ/ml.)	Killing Time (Minutes)
Hollichen HQ 3300	
1000	<0.5
200	0.5–1.0
50	1.0–1.5
Sterwin #904	
1000	<0.5
250	<0.5
50	0.5–1.0
Laurodin acetate	
1000	<0.5
250	<0.5
50	4.0–5.0
C.P.C.	
1000	<0.5
250	<0.5
50	1.0–1.5

pounds could be considered to be significantly better than any of the others (see Table II).

Qualitative Measure of Substantivity. Broth dilutions of the compounds were prepared in duplicate. (A modified Rammelkamp (3) broth dilution was used in which the minimum inhibitory concentration M.I.C. was determined to within 0.1 γ/ml.). To each tube in one series of dilutions a sterile skin disc was added. Both sets of dilutions were incubated in a water bath at 37°C for four hours. The discs were then removed from the tubes and discarded. Each of the tubes received the same inoculum of *S. aureus* and all tubes were incubated at 37°C for forty-eight hours. (Inoculum: A twenty-four hour brain heart infusion broth culture of *S. aureus*-209 was standardized to 50% transmission (±2%) using the Lumetron Colorimeter. A 10^{-3} dilution in broth was made, and 0.1 ml. of this dilution was used to inoculate each tube.) After incubation the tubes were read macroscopically for growth and the lowest concentration of test compound inhibiting growth was reported as the end point (M.I.C.).

If the test compound was substantive to the skin tissue, the dilution series, which contained the skin discs, had its end point (M.I.C.) shifted to a higher concentration of the test compound. The greater this shift relative to the M.I.C., determined in tubes without addition of skin discs, the greater was the substantivity of the compound. The binding of the compound to the discs accounted for this difference in end point. This can be expressed mathematically as a substantivity potency ratio (*Sp*) for a given compound by the following formula:

$$\frac{D - M}{M} \times 100 = Sp$$

D = inhibitory concentration in series that had skin discs
M = inhibitory concentration in series without skin discs
Sp = substantivity-potency ratio

Comparison of the *Sp* for several compounds can be used for the selection of a compound based on skin substantivity (see Table III).

Quantitative Titration of Skin Substantivity. Each sterile skin disc was rehydrated, placed in 10.0 ml. of a known concentration (0.1%) of the test compound; mixed for one minute at 37°C and finally pressed with a 50 g. weight between two Microfiber Glass Prefilter pads* (one minute) to remove excess fluid. The disc was serially washed in each of

* Millipore Filter Corp., Bedford, Mass.

TABLE III
Determination of Substantivity-Potency Ratio (*Sp*) for each of Test Compounds

Compound	*D* (mcg./ml.)	*M* (mcg./ml.)	*Sp*
Hollichem HQ 3300	0.90	0.70	28.6
Sterwin #904	0.60	0.45	33.3
C.P.C.	0.55	0.35	57.1
Laurodin acetate	0.65	0.40	62.5

TABLE IV
Quantitative Substantivity Measurement of Test Compounds Titrated Against *S. aureus*-209

Compound	Concentration (γ/ml.)	Test Rinse Showing Inhibition
Hollichem HQ 3300	500.0	0
	250.0	0
	125.0	0
	62.5	0
Sterwin #904	500.0	4
	250.0	0
	125.0	0
	62.5	0
Laurodin acetate	500.0	8
	250.0	2
	125.0	0
	62.5	0
C.P.C.	500.0	7
	250.0	2
	125.0	1
	62.5	1

15 broth tubes containing 5.0 ml. of broth. All tubes were inoculated with *S. aureus*, incubated at 37°C for seventy-two hours and read macroscopically for growth. (Inoculum: A twenty-four-hour brain heart infusion broth culture of *S. aureus*-209 was standardized to 50% transmission (±2%) using the Lumetron Colorimeter. A 1:10 dilution was prepared, and 0.2 ml. was used to inoculate each tube.) The rate of elution was correlated to the number of consecutive rinse tubes in which visible growth is inhibited at the concentration used. If the compound was not eluted from the disc, inhibition of bacterial growth did not occur in any of the rinse tubes. If the compound was eluted slowly, bacterial growth was inhibited in a large number of tubes. If the compound was eluted rapidly, bacterial growth was inhibited in a smaller number of rinse tubes.

Discussion

From the data obtained in the bacteriostatic and bactericidal tests (Tables I and II), it was evident that there was no significant difference in the antimicrobial activity of the four test compounds. Each of the four compounds was effective against a spectrum of microorganisms in the absence or presence of horse serum, and low concentrations of all the compounds were bactericidal. Hence, these criteria did not offer a means of judiciously selecting any one compound from the group for topical use. However, the skin substantivity results offered a means not only of selecting compounds for topical use but of selecting the compound best suited for a specific need.

The data presented in Table III indicated that all four compounds were substantive to the skin tissue and that C.P.C. and Laurodin acetate had a greater avidity for the skin than either of the other two compounds. If the only criterion for selecting a compound for use in a topical preparation were the property of skin substantivity then these data (Table III) would be sufficient for selection of the best compound for topical use. If the criteria for selection of a compound are extended beyond the property of skin substantivity to include the elution characteristics of active material, additional data would be required. Such data were obtained by titration of the active material released from the skin discs. The data in Table IV indicate that if the selection of a compound were to be based on the elution of active material for an extended period of time then selection of Laurodin acetate as the compound of choice would be indicated. If, however, the criterion for selection were the retention of the compound at the site of application then the selection of Hollichem HQ 3300 would be indicated. If rapid release of all or nearly all of the compound were desired, then the selection of Sterwin #904 would be indicated.

Summary

Skin substantivity of quaternary antimicrobial agents, which may have utility for topical application, was studied by several methods. By use of the described methods, it was possible to determine whether an antimicrobial agent had calf skin substantivity. Once this fact was ascertained, it was possible to determine whether the compound was bound irreversibly to the skin; if not, it could be shown whether the active material was released rapidly or slowly from the skin. From such

information and from knowledge of the intended usage the selection of the compound best suited for a particular type of topical formulation can be made.

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The Contribution of the Resistant Cell Membranes to the Properties of Keratinized Tissues

E. H. MERCER, D.Sc., Ph.D.*

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Synopsis—Electron microscopy of hard (hair) and soft (epidermis) keratin suggests that modified cell membranes are cemented by a continuous layer in the former and by a patchy layer in the latter. These differences are related directly to the desquamating nature of epidermis and the persistent behavior of hair and nails. This intercellular "membrane complex" is more resistant to chemical attack than intracellular keratin but easily dissolved by tryptic or peptic digestion.

Introduction

The keratinized tissues are cellular tissues, i.e., they consist almost entirely of cells filled with keratin and with a very small amount of intercellular binding material. They are to be contrasted with the connective tissues where the intercellular material enormously preponderates and the properties of the tissue are effectively those of the *intercellular* fibers and colloidal matrix. To take one property as an example, the physical strength of a cellular tissue is the strength of the complex of the component cells and their adhesive connections. Thus in a keratinized tissue the physical strength depends on: (a) the strength of the intracellular keratinized protein, (b) that of the cell membranes

* John Curtin School of Medical Research, Australian National University, Canberra, Australia.

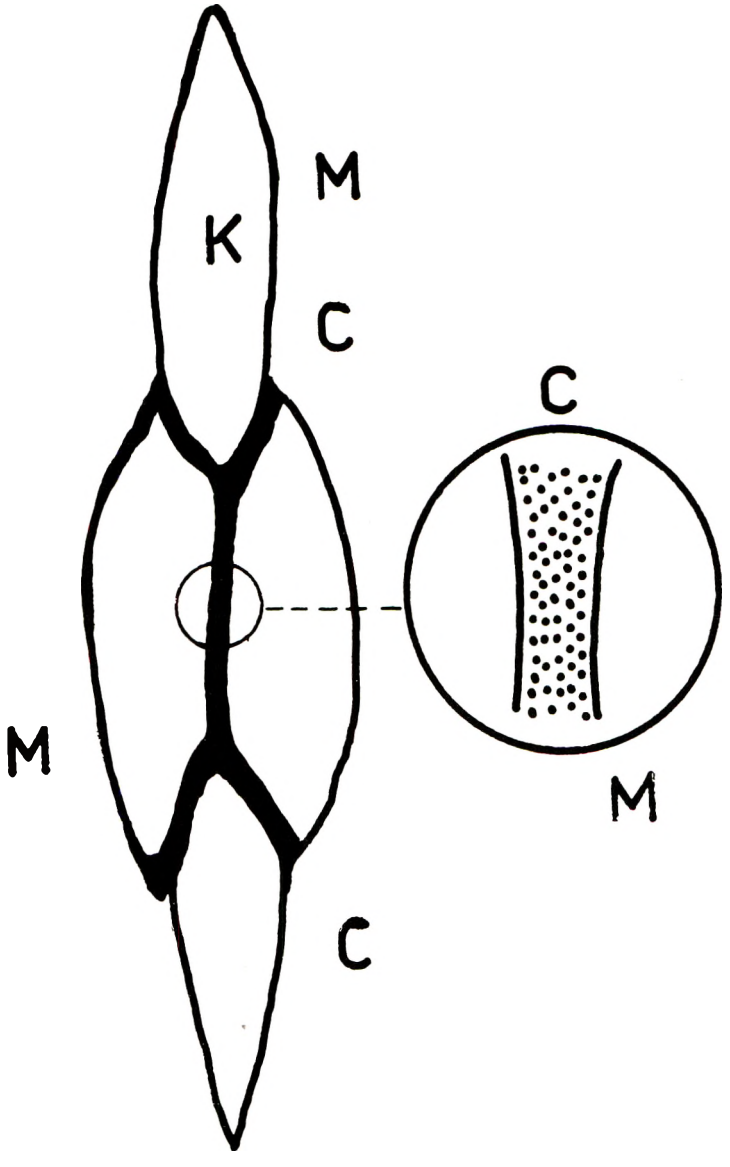

Figure 1. The relation between the keratinized cell contents (*K*), the resistant cell membranes (*M*) and the intercellular bonding material (*C*) in a keratinized tissue (here the hair cortex). Inset: the cell membrane-intercellular cement complex

enclosing the protein and (c) that of the intercellular cement, and these components are partly in parallel and partly in series (Fig. 1) (1). As with a chain this structure is no stronger than its weakest link.

The keratinized tissues are classified as desquamating (or soft) keratins (the epidermis) and the nondesquamating, hard and persistent keratins (nails, hair, etc.). This classification emphasizes an important functional distinction: the constantly growing epidermis maintains its near-constant thickness by disintegration into cellular fragments on its outer face, whereas the persistent nails and hairs are more permanent structures, which must be cut or worn away by use. In considering the coherence of these tissues we have clearly to take into account not only the properties of the protein (keratin) enclosed within the cells but also the properties of the cell membranes and the materials bordering them. Most of what we know concerning these matters comes from the study of hair (or wool), and this work will be summarized first. An account of similar investigations concerning skin will then be described. In each material we are concerned in the first place to establish the fine histology of the tissue and, second, to determine the chemical nature of each of the morphologically distinct components.

Cell Membranes and Intercelluar Material in Hair

That hairs were cellular tissues was appreciated by the earlier histologists, but the fact was often overlooked in the days when it was fashionable to regard a hair as a rod of a more or less uniform polymer, "keratin." A detailed description of the keratinized cells based on electron micrographs was given by the present writer and his colleague, Birbeck (2). The special chemical nature and the important role of the cell membranes was clearly recognized in this work, and since that time numerous other investigators have confirmed and extended these findings (3).

Briefly, the oriented bundles of intracellular keratinized filaments are enveloped by a modified cell membrane, which usually appears thicker than the original plasma membrane of the prekeratinized cells in the hair follicle but is clearly derived from it. These membranes are cemented together by rather uniformly thick sheets of some distinctly different substance, the whole forming what might be termed the "*cell membrane complex*." The cell membrane complex is effectively a continuous phase, a reticulum extending throughout the cortex of the hair and enclosing the keratinized filaments in its interstices (Figs. 1 and 2). When the hair is stretched, the membrane complex and the intracellular

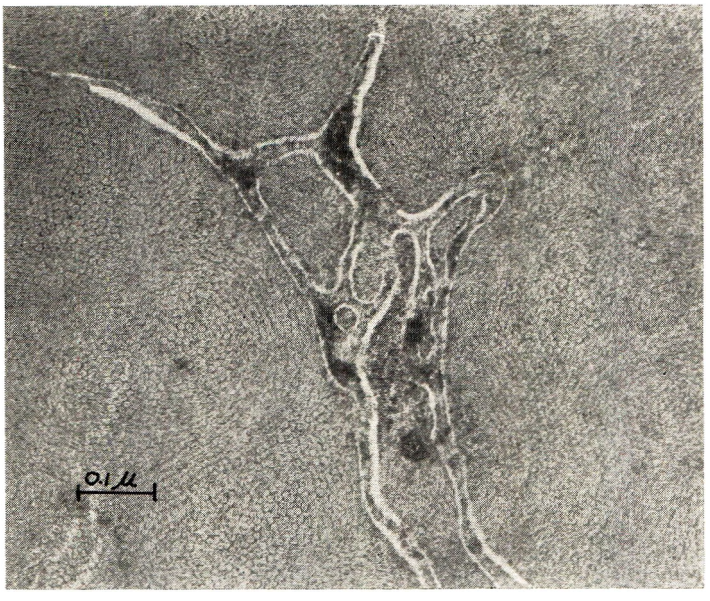

Figure 2. An electron micrograph of a cross section of hair (wool) showing the resistant membranes enclosing the bundles of keratin filaments. The membranes here appear light, being unstained by the method used. (photograph by B. K. Filshie)

filaments extend together, and the properties of both will contribute to the elastic properties of the whole hair. When a hair is treated chemically, the behavior of each of the components must be considered, since their chemical makeup proves to be very different.

The chemical resistance of the membrane complex proves in fact to be complementary to that of the intracellular keratin. That is, reagents or treatments which dissolve keratin do not dissolve the membrane complex; *vice versa*, the membranes may be removed without affecting the keratin. The biological advantages of this arrangement are obvious since the range of chemical environments against which a keratinized tissue offers protection is greatly widened. Keratin, owing its stability to disulfide bond cross linking, is very vulnerable to reducing and oxidizing agents and to alkaline conditions, which rupture this bond. It is precisely toward such conditions that the membrane-complex is resistant (see Table I).

The resistance (mechanical and chemical) of keratin has been frequently emphasized; the quite extraordinary chemical resistance of the altered cell membranes, which enclose the keratin as a bag encloses its contents, is not so commonly appreciated. We may well wonder what is

TABLE I

Chemical Resistance of Components of Hair to Various Reagents

Reagent	Intracellular Keratin	Membrane-Complex[a]
Sodium sulfide	Dissolves	Resistant
Sodium hydroxide (pH 11–12)	Dissolves	Resistant
Sodium thioglycolate, pH 11	Dissolves	Insoluble
Thioglycolic acid plus 10 *N* urea (pH 6–11)	Dissolves	Resistant
Peracetic and/or performic acids followed by alkali	Dissolves	Resistant
Hydrogen peroxide and alkali	Dissolves	Resistant
Tryptic and peptic digestion	Resistant	Dissolves

[a] The chemical behavior of medulla (when present) is like that of the membrane-complex.

the nature of a biological material which is resistant to: 10 M urea containing various reducing agents, caustic soda of pH > 12, cuprammonium sulfate, strong sodium sulfide solutions, etc. In fact, no true solvent for these membranes is known; yet their protein basis is revealed by the ease with which they are broken down by proteolyic enzymes.

When wet, the membraneous ghosts remaining after the keratin has been removed from any of the keratinized tissues have a long-range rubber-like extensibility about five times that of the oriented fibrous keratin of hair (100% extensibility).

The chemical basis of the unusual resistance of the membrane complex therefore remains to be established. One of the principal difficulties is to separate it in a pure form for chemical analysis. Relatively pure membrane-complex can be prepared by Alexander and Earlands' method (4) (oxidation by peracetic acid followed by alkaline extraction of the oxidized keratin, cf. Fig. 2). It is contaminated by traces of keratin and by remnants of the cellular apparatus of the cells (nuclei, mitochondria, etc.), the whole accounting for about 10% by weight of the fiber. If it proves to contain disulfide bonds like keratin itself, these must be in some sterically sheltered position where they are not reduced by keratinolytic agents; possibly some unrecognized bond is present.

Cell Membranes and Intercellular Material in the Epidermis

The duplex structure (intracellular keratin filaments plus resistant membrane-complex) is characteristic of all the keratinized tissues (5, 6). The hard keratins are essentially like hair. The epidermis, however, proves to have special features, which are apparent in electron micrographs of the intact tissue and in those of the resistant components separated from the tissue after extraction with a keratinolytic reagent (7).

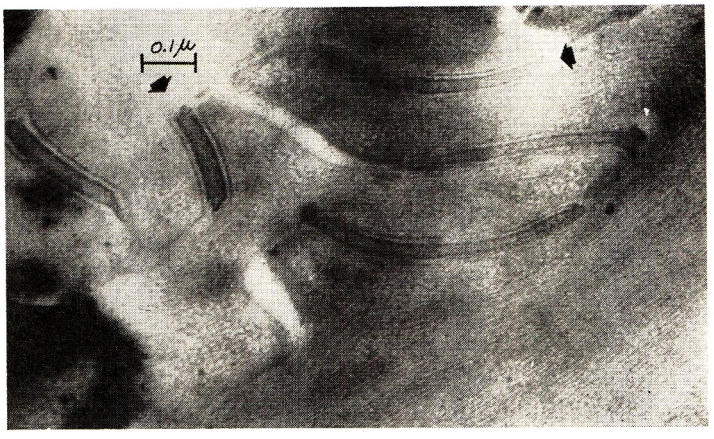

Figure 3. An electron micrograph of a section of the stratum corneum (human) showing the limited development of adhesive patches (at arrows). Compare with the continuous layer of bonding material in hair (Fig. 2)

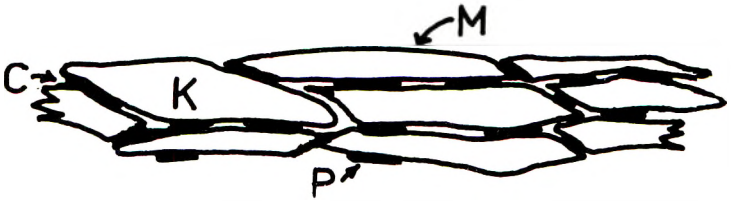

Figure 4. Drawing illustrating the patchy nature (*P*) of the intercellular adhesive (*C*) substance in the upper layers of the stratum corneum (M-cell membranes, K-keratinized contents of cells)

The intercellular bonding material (also called cement) in the hard keratins is a more or less continuous layer about 400–600 A thick, and it is essentially unaltered by the removal of the keratin (Fig. 2). In the keratinized epidermis, in contrast, this layer is discontinuous, being limited to discrete patches which unite the two opposed membranes over only part of their entire surfaces (Figs. 3 and 4). These rounded patches (1–2 μ) in diameter can be pictured as flattened balls of adhesive slipped between the cells. In fact, this seems to be what they are, since they originate within the cells as the contents of closed sacs and open onto their faces, as has been shown recently by Matoltsy and Parrakal (8). These rounded patches can be seen (Fig. 4) as numerous small studs on the surfaces of isolated epidermal cells after special staining (9).

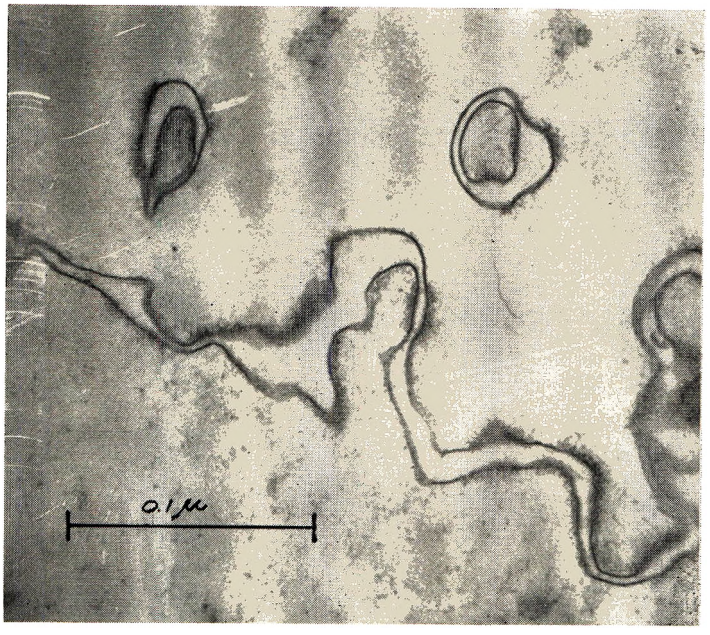

Figure 5. Electron micrograph of resistant membranes isolated from epidermis. Note: the membranes have separated, and the intercellular adhesive patches have been dissolved. Cf. Fig. 3

When membranes are isolated from epidermis by the same methods used to separate them from hair, a further difference emerges. The intercellular adhesive layer in hair is insoluble, and the separated membranes remain adherent, as described above (Fig. 2); the adhesive patches in skin are, however, dissolved, and the membranes separate (Fig. 5).

Similarly, the membranes in hair never separate during the normal lifetime of the tissue; the tissue is nondesquamating. The cells of epidermis of course separate, and the tissue desquamates. Electron micrographs of the superficial layers show that the membranes themselves persist, the breaks occurring in the adhesive spots (the keratinized contents also begin to fray). Thus this characteristic property of epidermis can be traced down to the properties of the adhesive patches between the cells (Fig. 4).

Some Reflections

From the observations described above, it is clear that our understanding of a keratinized tissue will remain incomplete until the chemical nature of the intercellular cement substances and the altered cell mem-

branes are known. The first step is the separation of each of the components in a pure form and in adequate amounts. An adequate analysis should answer the following questions:

(a) What chemical events occur during keratinization to change the labile phospholipid-protein complex of the living cell membrane into the extraordinarily resistant substance found in the hardened tissue?
(b) Similarly, what is the chemical composition of the resistant intercellular bonding substance which unites the altered membranes?
(c) What is the chemical difference between the intercellular material in hair and that in epidermis, which causes one to be permanent and the other to disintegrate?

These separations have been attempted and have not proved entirely satisfactory up to date; they could probably be perfected were effective use to be made of electron microscopy to control the purity of the preparations. Hopefully, we can look forward to having answers to the above questions before too long.

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Success and Failure of Odor Classification as Applied to Reactions to Erogenous Odors

ERNST PAUKNER, Ph.D.*

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Synopsis—One of the problems of successful perfuming is the difficulty of obtaining from consumers an indication of their ideas about the ideal fragrance, appropriate to the product under consideration. An interviewing method is described which reliably defines the consumer's ideal of the desired perfume type. This method (semantic differential) is illustrated with a description of the concept of an "erogenous fragrance."

Several single odorants, at different concentrations, and some well-known perfumes are included in the test. The data are analyzed by factor analysis to determine which of the materials comes closest to meeting the expectation of the ideal. The Henning and the Crocker-Henderson methods, traditional systems of odor classification, are evaluated and shown to be less suited for the determination of odor qualities.

Introduction

Early this year, it was reported that work is in progress in India and England on a perfume which is to serve as an adjunct to birth control measures (1). This perfume, when used by Indian women, is supposed to have the same kind of effect on Indian men as a repellent has on mosquitoes: it is, therefore, an antierogenous perfume. When he smells it, "Romeo no longer longs for Juliet," according to B. L. Raina, Director of the Indian Institute of Family Planning. On the other hand the concern of the perfumers in the Western world has been the

* Laboratories of drom, Bertelestrasse 75, München-Solln, Germany.

creation of fragrances which will make Romeo long for Juliet. In this paper the results of an investigation of the psychology of erogenous fragrances will be presented.

Consider, for example, the case of a manufacturer who is trying to attain broad public acceptance for a line of cosmetics. He is searching for an erogenous fragrance. This fragrance should give the woman who uses products with this fragrance the conviction that she is irresistible.

With the help of his marketing research department or an outside consultant organization, the manufacturer will be able to determine the most appropriate advertising theme, the most enticing package and the most effective merchandising approach. He can also find out whether, for example, a product in powder form or a liquid would be more convincing. Modern interviewing techniques can assess the feelings of potential customers in questions of this kind quite accurately. However, up till now the cosmetics manufacturer has had no way of getting a description of the most important thing in this case: the most effective fragrance for his product.

The reason why market researchers find it so difficult to establish the character or message of a perfume is the lack of words to describe this message. It is easy for a respondent to state in an interview that there should be a little less blue in a shade of violet which is meant to harmonize with an erogenous product. But how could he describe how a perfume should be changed in order to meet his expectations? Experienced market research specialists indicate that they know of no reliable method to determine either the impressions and feelings evoked by a fragrance or the consumer's image of the ideal fragrance for a given product.

As a result of the difficulty in finding out what the consumer wants, rather haphazard methods are still being used in fragrance selection. Instead of asking potential purchasers what the odor of cosmetic products should be like, the procedure often consists in selecting among the many available perfume oils a few that are considered appropriate. Next, a few people with responsible positions in the company (or their wives) decide which of these the public will like best.

This method is unsatisfactory, since too many purely accidental factors are involved. In order to find a better approach a research program on the psychology of odor was started in these laboratories several years ago (2, 3). Lately, the specific aim in these laboratories has been the search for a reliable classification of odor characters and for an exact way of expressing similarity or differences between odors. If one looks for an odor which comes as close as possible to an ideal image, one has to

be able first to get a good description of the image and then to determine how closely actual odors approximate this ideal.

Several existing odor classification systems, including those of H. Henning (4) and of E. Crocker (5) were examined. Both of these classification systems offer the possibility of determining the degree of similarity between different odors by describing each as a composite of several so-called primary odors. Crocker offers materials which can be smelled as his primaries; Henning only gives six verbal descriptions. His odor prism, constructed from these descriptions, is shown in Fig. 1.

It was found that certain odors can be reliably described within the systems, while for others it appears impossible to get any close agreement

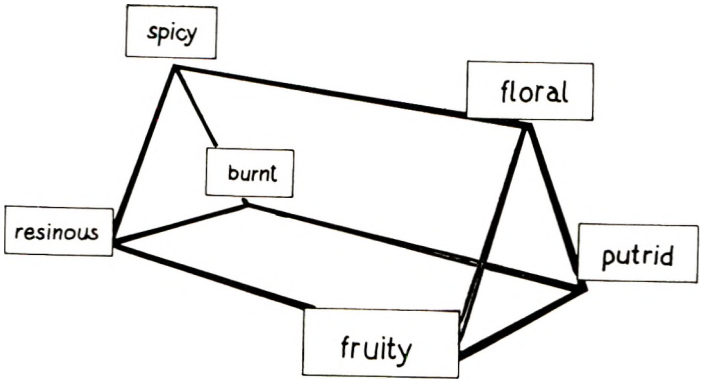

Figure 1. Henning's odor prism

between descriptions (in terms of primaries) by different subjects. Moreover, the primary odors of Henning or Crocker appear to be selected at random and give no clues regarding the psychological or emotional effect of odors.

Methodology and Discussion

Before an attempt is made to describe an erogenous fragrance one point should be stated clearly: An erogenous fragrance is not comparable to an aphrodisiac with purely physiological action. Instead, an erogenous fragrance is primarily related to emotions and to mental images which may be evoked by olfactory stimuli.

The odor of a perfume or some other odor might certainly strike one as erogenous. Certain perfume materials, such as musk or amber, are said to have a distinct effect of this type. Actually, perfumers have several other materials in their palette which fall into this class.

The description of some perfume materials as erogenous does not mean that these materials by themselves elicit the desired response. As will be shown further on, they do this only in combination with other odorants.

Neither Henning's nor Crocker's classification system can be used to find or describe an erogenous fragrance or to compare it with similar

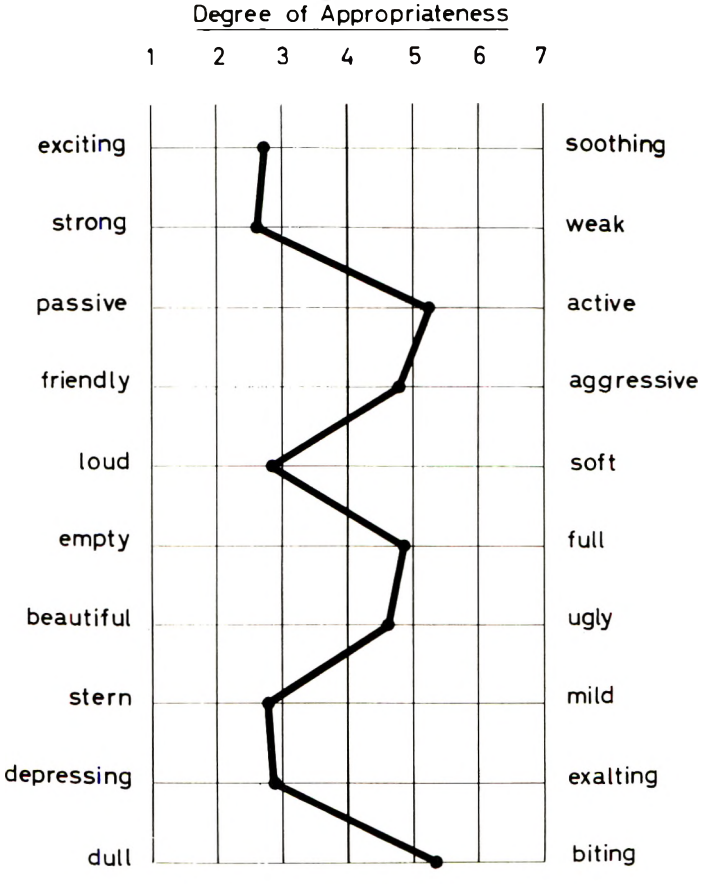

Figure 2. Partial profile of amber

fragrances. In collaboration with Prof. K. Eyferth of the psychology department of the University of Hamburg and Dr. R. Randebrock, Hamburg, a method of classifying fragrances which does meet these demands was developed. This approach is based on the "polarity profile" method of Hofstatter (6) (which corresponds to the "semantic dif-

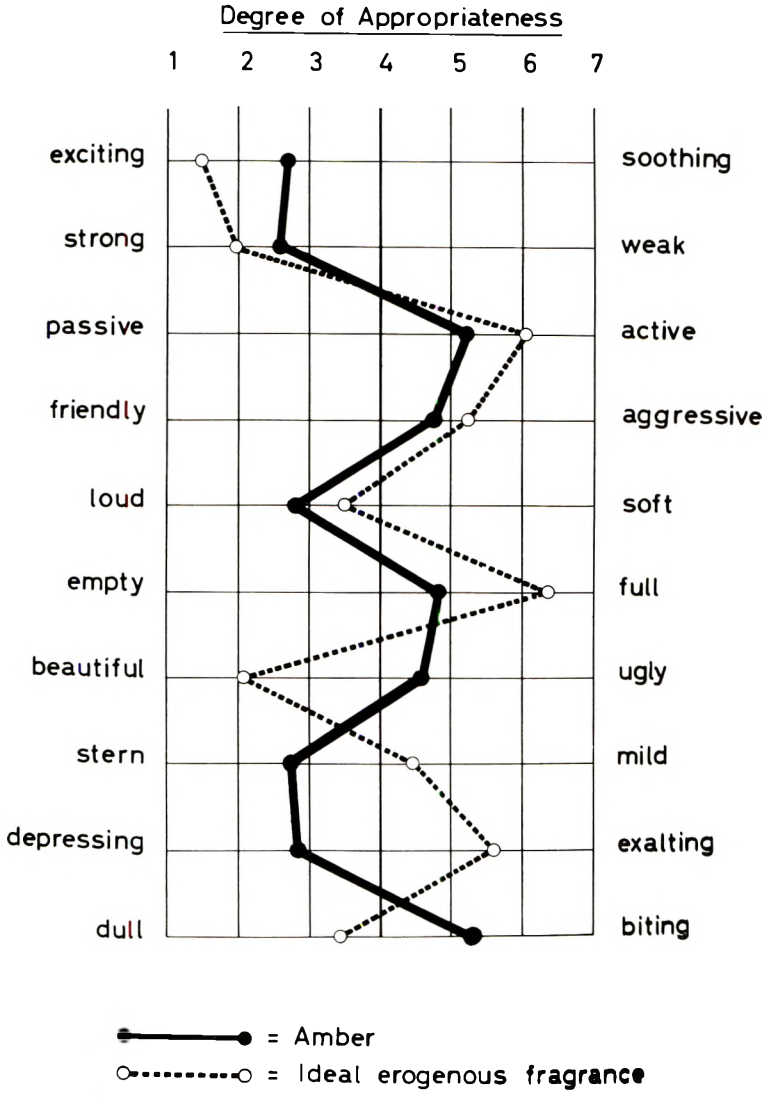

Figure 3. Partial profiles of amber and of "the ideal erogenous fragrance"

ferential" method described by Osgood (7) adapted to the specific demands of odor description). It was first employed in the study reported by the author in Munich in 1960 (3).

The heart of this procedure is a list of 29 pairs of adjectives; the two members of each pair are opposite in meaning.* Thirty judges were

* This list was obtained from an original list of 40 word pairs by eliminating those which, by use of the statistical "t-test," were found not to distinguish significantly between different odors.

asked to describe the odor of amber in terms of this list. Thus for the first word pair they expressed their opinion that amber is more exciting than soothing, in the seventh they found it more ugly than beautiful and so on down the line with all the other word pairs. Figure 2 shows the average of the 30 judgments on each word pair. The profile which is obtained in this way is typical for amber. It is, moreover, reproducible. The correlation between profiles obtained for amber at

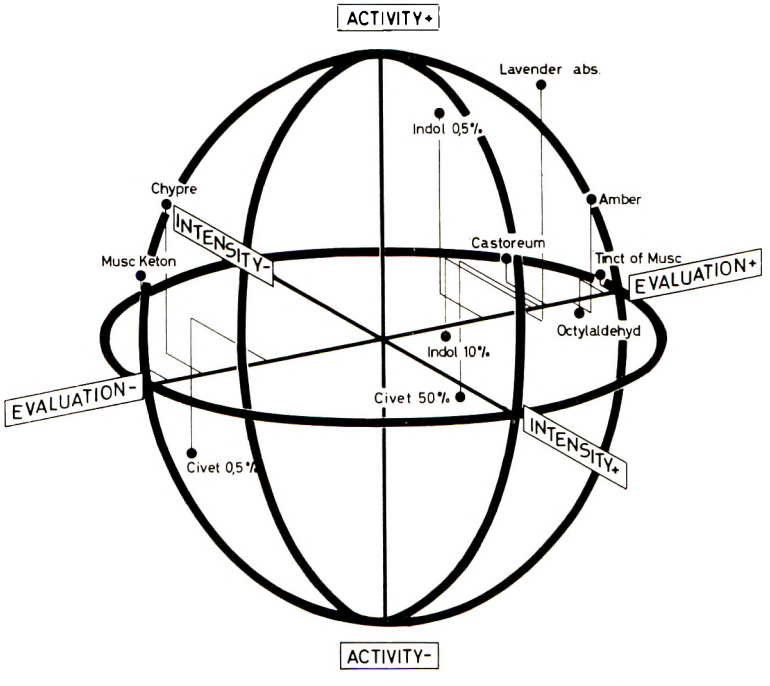

Figure 4. Odor description space with 11 "erogenous" odors

different occasions and by different judges lies between +0.87 and +0.94; the statistician knows that this is excellent.

One of the advantages of this method is that it can be used also to get a picture of concepts or mental images which have no physical reality. Thus 30 persons, who had first been asked about amber, were asked to imagine that fragrance which would most closely approximate their idea of erogenous and to describe it using the semantic differential.

The resulting profile has been partially reproduced in Fig. 3; clearly it is very sharp and characteristic. It now becomes possible to compare the profile of amber or of any other fragrance with this "ideal" profile.

The objective can now be expressed as the task of finding that fragrance the profile of which most closely approximates the ideal profile for an erogenous perfume.

When comparing two profiles, the correlation can be calculated to give an exact measure of the similarity of the two odors or of the similarity between a perceived odor and a mental odor-image. Using statistical methods and with a sufficient number of odor profiles Thurstone's (8) factor analysis can be applied. This analysis indicates how

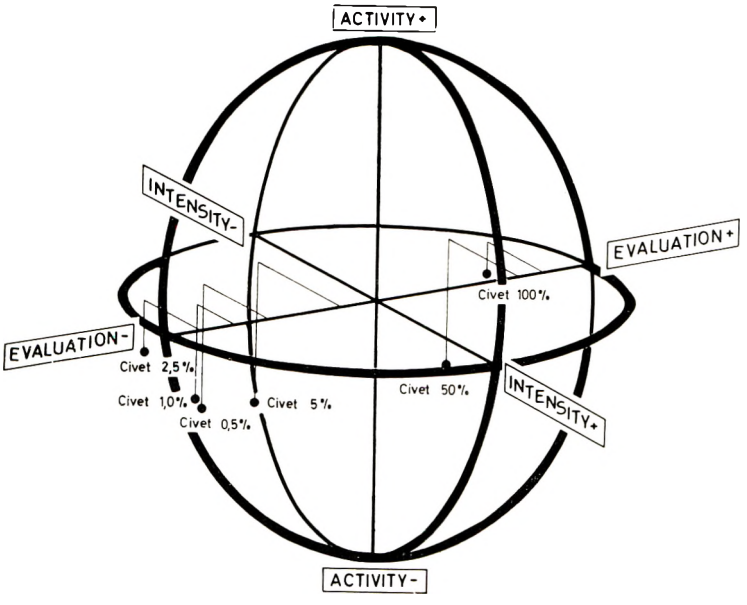

Figure 5. Position of different concentrations of Civet in odor description space

many mutually independent "dimensions" of odor description were distinguished by the judges. When 83 profiles of single aromatics, essential oils and perfume compounds were analyzed in this way it was found that all odor descriptions could essentially be reduced to three dimensions.

Translation of the obtained odor profiles into these three dimensions yields a means of describing findings in a simple picture. An *odor description space* can be constructed, the coordinate axes of which are the three odor dimensions derived from the factor analysis of odor profiles (Fig. 4). The first of these dimensions might be described as *evaluation:* it is a measure of how much the judges like the odor and to what extent

they find it "beautiful" or "harmonious." The second dimension is an expression of the *activity* of the odor and includes judgments on spiciness, alertness and strength. The third has to do with *intensity* of the odor; freshness, hardness and agressiveness ratings are found in this dimension.

Any given odor (the profile of which has been determined) can be indicated by a point in this odor space. This yields a method of comparing odors (or comparing actually perceived odors and "odor-images") which is more meaningful than the correlation coefficient of odor profiles: Their position in the odor space can be compared, and the distance between them in this space can be calculated. In Fig. 4 is shown the position in the odor space of 11 odors which are generally considered erogenous by perfumers. The location of each point was calculated from polarity profiles (semantic differentials) obtained from thirty judges. It can be seen that these 11 odors do not have very much in common. They are distributed over the entire odor description space. It will be noticed, for instance, that Tincture of Musk (5%) is judged nearly exclusively in the evaluative dimension; it is characterized by high ratings on "disharmonious," "unpleasant," "ugly," "stale." By contrast, Lavender absolute (1%), with high ratings on "happy," "fresh," "young," "interesting," "spicy" and "bright," scores primarily in the second dimension, activity. Civet was first smelled in two widely different concentrations, 0.25 and 50%, and it is notable that the position of Civet in the odor space changes drastically with concentration. This made it desirable to run further tests to obtain the profiles of Civet at four additional concentration levels, and in the end values for different concentrations of Civet (0.5, 1.0, 2.5, 5.0, 50, and 100%) were entered in the diagram (Fig. 5).

The six points for Civet do not lie very closely together at all, a fact which will not surprise the experienced perfumer. The same observation can be made for other odorants which are considered erogenous by the general public, such as amber and musk. Apparently no single odorant, be it of animal, vegetable or synthetic origin, possesses a clear-cut erogenous effect. In high concentration nearly all of the materials in question are described as unpleasant and aggressive. The perfumer knows from experience that it usually takes very small proportions of strong, often disagreeable, even fecal odors to achieve an erogenous effect in a blended perfume. This fact was first pointed out and explained by Jellinek (9).

To test the described method, a relatively neutral perfume of a simple lavender type was developed (Step 1). By adding 15% of an "animal" perfume oil composed of nitro musks, civet and synthetic amber an attempt was made to achieve a noticeable erogenous touch (Step 2). Step 3, aimed at a maximal erogenous effect, was made by adding 40% of the "animal" compound to the basic lavender composition (Fig. 6). The positions of these three compounds are not too far removed from one another. If the point which characterizes the ideal concept of an erogenous odor is taken into consideration it becomes ap-

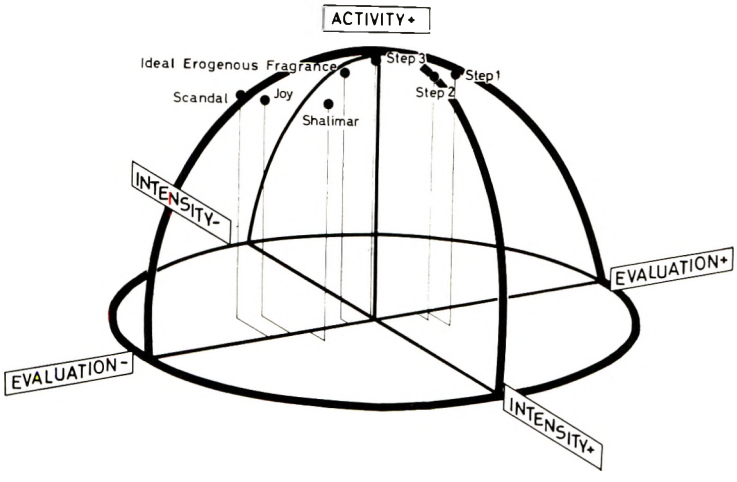

Figure 6. Odor description space showing experimental approach to ideal erogenous fragrances and some commercial perfumes

parent that the stepwise additions did indeed result in a progressive approximation of the judges' mental image of an erogenous odor.

An obvious thing to try at this point is to find out where the modern French luxury perfumes fit into the odor space. This would be a way of testing whether these creations are more distinctly erogenous than are other perfume compounds. With the consent of the manufacturers, the three well-known perfumes, "Shalimar," "Joy" and "Scandal" were selected (Fig. 6).

Although these perfumes are quite different from one another (and although the judges did not know the names of the perfumes), an analysis of the profiles showed that all three were considered to be quite close to the image of the ideal erogenous fragrance. This is not too surprising in view of the reputation of these perfumes. Still, the results are valuable since they constitute, more nearly than any data heretofore available, an objective proof that these perfumes represent a close ap-

proximation to the consumers' ideal. Moreover, the experiment confirms that the erogenous message of these luxury perfumes comes across, even when the person smelling them has no extraneous clues such as the name of the perfume or its advertising copy. Furthermore, a rather interesting and amusing observation was made: not only with these perfumes but with all odor tests there were no statistically significant differences between the reactions of male and female judges.

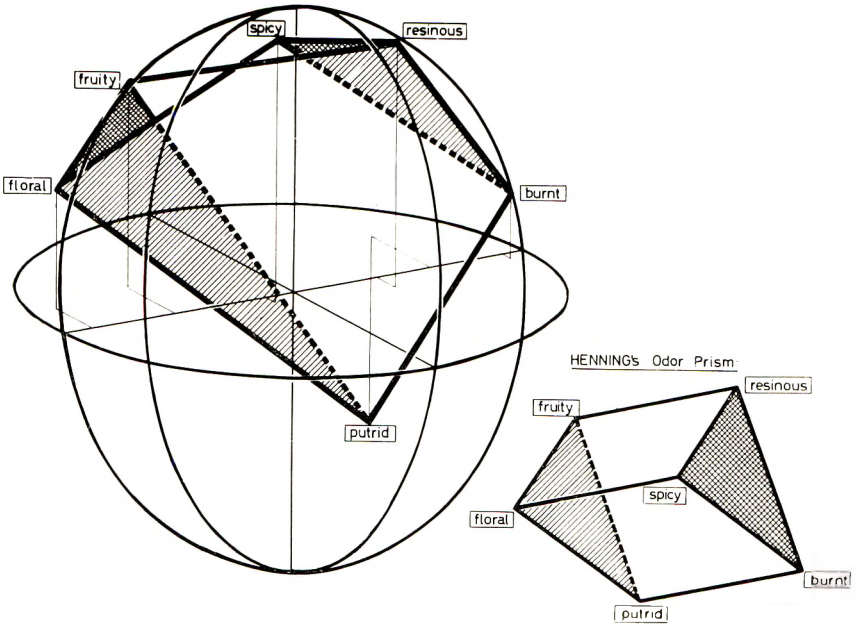

Figure 7. Henning's odor prism in odor space

Nor was there any relation between the resulting profile and the personality type, hair color or age, educational level or socioeconomic status of the respondents.

Such proof as was achieved here could not have been accomplished by the use of existing classification systems such as those of Crocker, Henning or Zwaardemaker (10). Nevertheless, reference will be made once more to Henning's system, devised nearly 50 years ago. Henning's prism was examined in the light of the semantic differential technique by asking judges to draw up the profiles of their concepts of Henning's six primary odors: fruity, floral, spicy, resinous, burnt and putrid. If Henning's system were compatible with the one described here, then

the points representing his primary odors should occupy positions in the odor space such that a prism would be formed by connecting them.

The diagrams show that this is not the case. On the right, Henning's prism is shown in its theoretical form, on the left the way it appears from the odor profiles of the judges; it does not form a prism. The majority of known odors cannot be described by use of Henning's six primary odors.

Crocker was inspired by Henning's work to develop a revised model. He assumes the existence of only four basic odors: acid, fragrant, burnt and caprylic. Each odor is described by indicating, on an eight-point scale, to what extent each primary odor is a component of the odor being described. A serious weakness of this system, as Ross and Harriman (11) pointed out, lies in the fact that there is no proof that these four basic odors really represent those characteristics which make one odor different from another. Moreover, the use of only four characteristics leads to an unstable profile; in practical use, it is not reproducible. It was found that stable profiles could be obtained only through the use of a large number of polarities—29 in the case described here.

It must be concluded that the traditional classifications of odors fail to provide the means for a reliable description of odor impressions or of mental images of fragrances. This was one of the reasons why an attempt was made to develop a new method which would be useful as a guide to the development of appropriate and successful perfumes.

Summary

In the field of fragrance it is feasible to obtain a description of a mental image of an ideal. It is feasible also to determine to what extent an existing fragrance approaches this ideal. In Western culture there exists a definite image of the ideal erogenous fragrance. Using the described method, which was developed in cooperation with Prof. K. Eyferth and Dr. R. Randebrock, it is possible to create fragrances which come close to this ideal. This odor-psychometric method is, in several ways, more practically useful than the classification system described in the literature. It permits an insight into the fine structure of the world of odor perception, a world which is complex and mysterious even for the expert.

The data obtained by the use of the semantic differential method, in spite of the subjectivity of the individual judgments which make up the profiles, are reproducible and in a sense objective and reveal the existence

of relations which seem to have general validity. These data make possible the selection of the most appropriate fragrance, the one which most closely approximates the recognized ideal image. If the manufacturer, market researchers and psychologically trained perfumers cooperate in the search for the most effective perfume for a given product, this new method can become a powerful tool in the search.

The method is new and stands at the beginning of its development. Frequent practical application will certainly lead to further improvements and refinements. But even at this early stage, its advantages are apparent: chance or the taste of a few individuals—obstacles in the selection of a truly appropriate fragrance—are eliminated, and the decision is based squarely on the verdict of potential buyers and users of the product.

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Dermal Connective Tissue Alterations with Age and Chronic Sun Damage*

J. GRAHAM SMITH, JR., M.D.,
and G. ROLLAND FINLAYSON, M.D.†

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Synopsis—The changes in human Caucasian skin commonly believed to be due to aging are primarily the effects of prolonged repeated damage to the skin from the sun. Covered aged skin shows marked differences histochemically and biochemically from exposed aged skin. With aging there is a decrease of nonfibrous protein and of soluble collagen, although the total collagen increases. The total acid mucopolysaccharides decrease, especially hyaluronic acid. In chronically sun-damaged skin (actinic elastosis) there is little change in the amount of extractable soluble collagen. The insoluble collagen content is reduced to one-third of that of control skin, and there is an increase in an elastin-like protein. Total acid mucopolysaccharides increase in actinic elastosis, especially hyaluronic acid.

Introduction

Exposure of susceptible Caucasians to the elements, especially sunlight, is more important than age in producing the clinical changes of actinic elastosis—wrinkling, loss of elasticity, and histologic changes in the dermis. This has been appreciated by careful investigators of the problem for over 75 years (1), and confirmatory studies have been reported by many investigators (2–5). Indeed, Benjamin Franklin (6) in

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† Division of Dermatology, Department of Medicine and the Center for the Study of Aging, Duke University Medical Center, Durham, N. C.

1745 may have been alluding to this when he stated that " . . . covering all above with a basket, and regarding only what is below the girdle (waist), it is impossible of two women to tell an old one from a young one" since the changes of actinic elastosis which are so commonly interpreted as changes of age are not observed clinically or histologically in unexposed areas such as the lower abdomen and buttocks.

Pigmentation of the skin represents a natural protective mechanism from these changes, and it is a common clinical experience to have difficulty judging the age of Orientals and Negroes, both of whom show much less severe changes in the exposed skin with age. This paper will review the histologic and biochemical alterations occurring in the dermis with age and chronic sun damage (actinic elastosis).

Aging and Sun Damage

I. Histologic and Electron Microscopic Changes

In reviewing the literature concerning cutaneous aging changes, it is sometimes difficult to be sure that investigators have appreciated the striking differences which may occur in exposed skin as compared with covered skin. With age, few histochemical changes are observable in the human dermis. Small decreases in neutral and acid mucopolysaccharides are associated with thickening and coarsening of the collagenous fibers (7). Few dramatic changes are seen in the elastic fibers, although there appears to be a slight increase in the skin of adolescents and adults as compared to premature infants.

Sun-exposed skin from Caucasians shows dramatic changes; indeed, the changes are seen to a lesser extent in exposed skin from Negroes (3). Using the periodic acid-Schiff stain after diastase digestion for neutral mucopolysaccharides and the Mowry colloidal iron or alcian blue stains for acid mucopolysaccharides, there are increases in neutral and acid mucopolysaccharides (8, 9). In the upper portions of the dermis, there is marked basophilia with toluidine blue and atypical staining with the van Gieson, aniline blue, phosphotungstic acid hematoxylin (8), and luxol fast blue stains (10). Elastic tissue stains such as orcein, Verhoeff's, and aldehyde fuchsin stain the fibers heavily in the upper dermis (11, 12). These fibers which stain like elastic tissue are digested by elastase but not by collagenase or crystalline trypsin (11). If these fibers were collagen, they should be digested by collagenase, and if they were degraded collagen, they should be digested by both collagenase and trypsin (13). The lack of susceptibility of these fibers to either collagenase or trypsin is

strong evidence that this material is more like true elastic tissue rather than a form of degraded or degenerate collagen. The fibers in actinic elastosis also look like elastic tissue rather than collagen in the electron microscope (14, 15).

A puzzling aspect of actinic elastosis is the presence of a "Grenz" zone in the papillary area just beneath the epidermis (8, 12). This consists of normal appearing and staining delicate collagen fibers, argyrophilic fibers and fibroblasts with little or no elastic tissue.

II. Ground Substance

The ground substance or aqueous matrix in which the fibrous proteins of the dermis are embedded makes up 5 to 10% of the dry weight of the dermis (16). Since the total carbohydrate content of the dermis is approximately 1% of the dry weight and the total acid mucopolysaccha-

TABLE I

Acid Mucopolysaccharide (Amps) in Human Skin (μm Uronic Acid via Orcinol/g. Dry Weight)

	Premature Infants	Term Infants	Children	Adolescent	Adult	Actinic Elastosis
Hyaluronic acid	6.0	5.0	3.8	0.61	0.9	3.2
Chondroitin sulfate	4.7	4.2	1.0	0.96	1.3	1.6
Total AMPS	10.9	9.5	4.9	1.8	2.4	5.2

Modified from reference 23.

ride content is 0.1 to 0.2% (17), obviously these components cannot represent markers for ground substance in the same manner that hydroxyproline does for collagen. Similarly, hexosamine cannot be used as a marker for acid mucopolysaccharides unless the acid mucopolysaccharides are first isolated from the dermis in a relatively pure form. Approximately half of the hexosamine in dermis is in serum proteins (18), while less than half is in acid mucopolysaccharides.

As a function of age, hexosamine does decrease in the dermis (19), probably reflecting the decrease in neutral and acid mucopolysaccharides found histologically. Biochemical studies of animals and man have demonstrated decreases in acid mucopolysaccharides occurring with age, especially hyaluronic acid (17, 20, 21). Conversely, in exposed skin, there is an increase in hexosamine, and it has been demonstrated that this increase is in the upper dermis—the area where the histologic changes of actinic elastosis are seen (22). Acid mucopolysaccharides are increased in actinic elastosis, particularly hyaluronic acid (17, 23) (see Table I).

TABLE II
Amino Acid Analyses of Human Dermal Fibrous Proteins (Residues/1000 Total Residues)

	Acetic Acid Soluble Collagen			Insoluble Collagen			Elastin		
	Premature Infant	Adult	Actinic Elastosis	Premature Infant	Adult	Actinic Elastosis	Premature Infant	Adult	Actinic Elastosis
Hydroxyproline	48.2	85.9	72.5	81.4	82.0	78.1	11.9	10.6	8.4
Aspartic acid	58.0	55.8	64.1	57.8	55.1	61.1	24.2	8.4	16.4
Threonine	28.0	21.8	33.1	17.4	23.8	14.9	16.0	8.2	13.2
Serine	55.9	46.2	83.9	29.4	51.6	28.5	20.6	8.5	13.9
Glutamic acid	90.4	77.9	81.9	87.6	75.4	88.2	61.2	21.7	28.1
Proline	86.7	112.2	92.4	116.7	111.8	112.8	115.1	122.2	114.4
Glycine	276.6	298.0	260.5	308.6	328.2	299.2	286.8	299.4	280.2
Alanine	101.8	105.6	89.8	99.5	115.1	108.3	183.9	243.0	230.0
Valine	35.1	27.8	39.4	29.5	14.3	34.7	104.5	142.0	132.9
Methionine	6.8	4.1	6.8	0.6	7.2	1.0	tr.	1.3	1.4
Isoleucine	24.2	16.7	21.0	17.2	11.0	18.7	23.8	24.5	26.6
Leucine	49.8	43.5	52.5	36.7	25.9	37.5	65.1	56.1	59.5
Tyrosine	13.9	7.1	13.7	11.5	4.4	9.0	12.3	10.7	14.1
Phenylalanine	22.6	17.3	21.0	16.4	18.7	17.4	24.7	21.9	22.7
Hydroxylysine	3.1	4.2	5.4	10.5	8.8	7.6	...	...	...
Lysine	37.7	26.1	28.9	29.8	31.9	30.5	30.6	10.1	14.8
Histidine	9.8	7.6	6.8	7.2	3.3	6.6	5.3	0.6	0.5
Arginine	55.2	45.4	26.3	43.2	38.5	45.8	12.1	7.2	11.0

Modified from reference 26.

The nonfibrous proteins in the dermis, an undefined mixture of serum proteins, glyco- and mucoproteins and other noncollagenous proteins, can be approximated and have been demonstrated to decrease with age in man. They are increased in sun-damaged skin (16).

III. Collagen

Collagen makes up one-third of the total body protein, and half of the total collagen is in the skin. As a function of age, the total amount of collagen increases (16), and the collagen itself becomes more highly polymerized (24). This increased cross-linking of the collagen results in its decreased solubility and may represent an extremely important aspect of aging connective tissue throughout the body (25). In exposed, sun-damaged skin, the total collagen is decreased (16, 26). Utilizing different patients, variations in the amount of soluble collagen have been reported; however, the total collagen has invariably been found to be reduced. Amino acid analyses of soluble and insoluble collagen fractions from covered human skin of various ages and sun-damaged areas have shown minor differences within the range of experimental error (26) (see Table II).

IV. Elastin

With aging, there is a slight increase in elastin when premature skin is compared with adult human skin (26). There is, however, an enormous increase in elastin in sun-damaged skin, up to 13% of the dry weight of the skin as compared with 2% elastin in unexposed adult skin (27). That this is true elastin appears to be well established, based on its morphology, solubility, enzyme susceptibility, tinctorial and physical properties, and amino acid composition (28). Miller *et al.* (29) have recently demonstrated that lysine is the building block of desmosine and isodesmosine, important cross-linking components in elastin. They have also shown that lysine in elastin decreases progressively with age, while desmosine and isodesmosine increase. The finding of increased amounts of lysine in elastin isolated from sun-damaged skin as compared with unexposed adult skin elastin (see Table II) suggests that the elastin in actinic elastosis may be newly synthesized. Amino acid analyses in other respects are quite similar between premature, adult, and actinic elastosis dermal elastin (see Table II).

Discussion

The changes with age and chronic sun damage (actinic elastosis) are profound and quite different. Although the mechanism for these

changes is not known, hypotheses based on some recent studies may explain what is happening. Subcellular particles called lysosomes (30) have been demonstrated in fibroblasts and are known to contain collagenase (31, 32). Elastase has not been reported in such particles, and its only known mammalian source is the pancreas (13). The lysosomes are labilized by heat and ultraviolet light below 3100 A (33, 34). One might postulate that the labilization of these particles with release of collagenase leads to the digestion and thus reduction of the amount of collagen in the dermis following sun exposure. The extent of these changes, of course, would be dependent upon natural protection such as pigmentation and individual variability of the susceptibility of the lysosomes to labilization.

There are enzymes in lysosomes which degrade mucopolysaccharides (30, 35). Hyaluronic acid is also depolymerized by ultraviolet light below 3100 A (36, 37). The increase of hyaluronic acid may be a function of enzymatically degraded mucopolysaccharides being recycled metabolically while the collagen subunits are not. The lack of elastolytic enzymes in lysosomes as well as the lack of any direct effect or ultraviolet light (2900–3200 A) in degrading either collagen or elastin *in vitro* (38) could explain the increase in elastic tissue found in this disorder as new connective tissue, collagen *and* elastin, is synthesized to replace the digested collagen. It must be emphasized that it is not known if ultraviolet light in the crucial range of 2900–3100 A labilizes lysosomes.

The presence of the "Grenz" zone of normal appearing connective tissue associated with argyrophilic fibers just beneath the epidermis and the depth of the elastosis below the level of penetration of ultraviolet light from natural sunlight may be clarified by some recent studies in amphibia. Using ^{3}H proline Hay and Revel (39) have shown concentration of the label at the epidermal-lamellar junction, suggesting that newly formed collagen of the dermis is first deposited at this site. In the lamprey, the collagen fibrils nearest the epidermis are small (as in man), but in the deeper layers beneath the epidermis they become larger, presumably representing older more mature fibers (40). Therefore, it appears that the dermis and epidermis grow in opposite directions from each other, that is, the epidermis grows outward and the dermis grows inward, possibly pushing newly synthesized elastotic fibers along with it. Such growth of the dermis would satisfactorily explain a number of other observations such as: the fine delicate fibers in the papillary layer and the thicker coarser fibers in the reticular layer of unexposed skin; the argyrophilic fibers representing immature collagen fibers (41) in the

"Grenz" zone; the great depth of elastotic fibers in actinic elastosis below the level of penetration of ultraviolet light; the gradual increase of depth with time of agents used for tattoos; and the gradual decrease in hyaluronic acid with increased chondroitin sulfate B in the deeper layers of pig skin (42). The latter is a situation analogous to the association of infant skin with more hyaluronic acid than chondroitin sulfate B and skin from the elderly with the reverse pattern (23). This also suggests that actinic elastosis may be partially reversible by avoidance of further sun damage since new connective tissue is forming continually at the epidermal-dermal junction and growing downward. Regression of the changes of actinic elastoses in transplanted actinically damaged skin has been reported (43).

It is difficult to explain why a substance such as topically applied testosterone, which is thought to act by increasing the acid mucopolysaccharide content in the dermis, produces changes which are interpreted as reversal of sun damage effects in the presence of already increased dermal acid mucopolysaccharides (44). This may be due to the degree of polymerization and molecular weight of newly synthesized polysaccharide.

At the present, the only practical approach to the cosmetic problem of actinic elastosis appears to be avoidance of excessive exposure to the sun and use of artificial sunscreens. The synthesis of new connective tissue following injury of the skin by surgical planing or caustics such as trichloroacetic acid or phenol is a more drastic approach whose value is still not adequately defined (45).

Summary

Histological and biochemical alterations in aging and sun-damaged human dermis (actinic elastosis) are quite different. Aging changes are characterized by decreases in nonfibrous protein, acid and neutral mucopolysaccharides, and slight increases in the fibrous proteins, collagen, and elastin. Sun-damaged skin (actinic elastosis) has marked increases in acid and neutral mucopolysacchride and elastin with decreased amounts of collagen. The prevention of changes due to chronic sun damage in susceptible individuals by the avoidance of excessive exposure to sunlight and use of artificial sunscreens is recommended.

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MAJOR MEETING DATES

1965–1966

September 14–15, 1965 — Annual Seminar
Ambassador Hotel
Los Angeles, California

September 20–21, 1965 — Joint Meeting S.C.C. U.S. and Mexico
Continental Hilton
Mexico City

November 30, 1965 — Annual Scientific Meeting
Hotel Biltmore
New York City

May 10, 1966 — Semi-Annual Scientific Meeting
Hotel Biltmore
New York City

June 27, 1966 — International Federation of Societies of Cosmetic Chemists
Paris, France

September 20–21, 1966 — Annual Seminar
Americana
New York City

November 30, 1966 — Annual Scientific Meeting
Hotel Biltmore
New York City

Book Reviews

EMULSIONS: THEORY AND PRACTICE by Paul Becher, New York, Reinhold Publishing Corporation. Second edition, 1965. 440 pages, illustrated and indexed. Price $22.

Most cosmetic chemists who deal with emulsions must be familiar with the first edition of this book, which was published in 1957. This review may therefore concern itself principally with the amount of useful new material in the second edition. First, let it be said that the new edition, like the original, is a well organized, concise, and incisive treatise by a physical chemist who has made distinguished contributions to both theory and application in this field.

The second edition is organized almost identically to the first, but Appendix B, which listed commercial emulsifying agents, has now been omitted because of the transient nature of such information. The new edition contains 93 more pages than did the old one minus Appendix B.

Appendix A of the first edition, covering tests for emulsion properties, is now the last chapter of the text and is lengthened by ten pages-the references cited here have increased in number by 77%, the largest increase in any chapter. Several new sections appear, including one on determination of HLB and of required HLB.

Chapter 7 on techniques of emulsification has also grown notably in the elapsed eight years. Its section on mixing time and general technique contains much new material, and the following sections have been added:

Emulsion type
Orifice mixing
High shear
Ultrasonic methods
Spontaneous emulsification
Microemulsions
Homogeneous emulsions.

Several new pieces of emulsifying equipment are pictured.

In Chapter 4 on theory of emulsions: stability, considerable new material is found, including:

a new section on viscosity of the interfacial film, and one on spreading coefficient and stability;

a new section on electrophoresis and zeta potential;
extensive reorganization of the material on double layer and potentials.

Chapter 2 contains more material than before on micelles, and Chapter 5 presents several new figures on emulsion inversion, new sections on the mechanisms of coalescence and of rupture, and several new sections on other phenomena of emulsification.

Chapter 6 includes the phosphate esters, fluorinated nonionics, and silicone nonionics in its treatment of emulsifying agents. It also contains a new 11-page section on the theoretical significance of HLB. The particle-size material of Chapter 3 is reorganized, and more material on viscosity has been added to this chapter on physical properties of emulsions.

Elsewhere, the newer data and concepts have been fitted into the framework set up for the first edition. The importance of the new material fully justifies the new edition, which cites 40% more literature references than the old and thus provides full and up to data coverage of material highly useful to the cosmetic chemist.

Under "Terminology" on page 2 we still find the arresting statement: "The disperse phase may also be referred to as the *nondisperse* or *discontinuous* phase." On the whole, however, errors are very few, and the paper and typography combine with the clarity of style to make the book easy to read.—PAUL G. I. LAUFFER—Chesebrough-Pond's, Inc.

THE STRUCTURE AND PROPERTIES OF BIOLOGICAL SYSTEMS, ADVANCES IN CHEMICAL PHYSICS, Volume VII, edited by J. Duchesne, Interscience Publishers, New York. 1964. 754 pages, illustrated and indexed. Price $27.50.

With this volume, this series ventures into the field of biology for the first time. It treats the field from the viewpoint of modern physics. A wide international array of authors have submitted chapters, and where necessary excellent English translations have been provided. The book is divided into a theoretical part and an experimental part, the over-all goal being to utilize quantum mechanics to try to establish quantitative relationships between biological activity and certain electronic and energetic molecular indices of biological molecules.

The theoretical chapters 1 to 4 deal with the properties of DNA, RNA hemoproteins and coenzymes. The other 14 chapters deal with a variety of experimental approaches to attempt to understand various biological molecules or systems. For example, the effects of ionizing radiations, hydration, and thermal responses are used to elucidate molecular structure. Model systems are subjected to careful measurements of their electrical and magnetic properties to explain the properties of more complicated biological compounds. The possibilities of modern spectroscopic methods are examined in dealing with complex biological systems in their natural aqueous environments. The detailed ex-

planation of the operation of biological mechanisms is attempted, using enzyme kinetics and physicochemical methods.

Over-all this book provides a very interesting review of a number of topics of great interest in current biological research by specialists in these fields. However, for the reader not directly involved with these particular topics, the treatments are usually too detailed and require too much effort to follow. Nevertheless, this volume gives the flavor of a field growing rapidly and making important contributions to our understanding of biological systems.—PAUL FINKELSTEIN—Gillette Medical Research Institute.

DERMATOLOGICAL FORMULARY AND PRESCRIPTION MANUAL by Morris Dauer and Irwin I. Lubow, International Professional Publications, Inc., Flushing, N. Y. 1964. 143 pages, indexed. Price $4.

The two authors have combined their efforts and experience in compiling a formulary which may serve to acquaint the medical student, resident, physican and specialist with medications commonly prescribed for the treatment of skin diseases. Furthermore, this manual can serve as a guide to the medical student in correct prescription writing.

This formulary is a compilation of old and new remedies collated from the various reference books, textbooks and medical journals. It is divided into six main sections. The first five consist of prescription items listed according to their generic or common name along with their respective tradename, name of the manufacturer and the available dosage forms and potencies. General precautions to be observed during the administration of these drugs are included for each section. These, however, are too concise. Before prescribing any of these products, the physician should acquaint himself with the therapeutic action, uses, administration, dosage, contraindications and possible side-effects.

The last section consists of extemporaneously prepared formulations and lists the individual components, concentrations, method of preparation, and, whenever necessary, packaging instructions. The therapeutic indications for groups of formulations are also included.

This book should prove to be a handy reference book to the medical profession and an aid for proper prescription writing to the medical student. However, this manual is of little or no value to the chemist or pharmacist. — M. STOLAR — Dome Chemicals, Inc.

THE PROTEINS, COMPOSITION AND FUNCTION, 2nd Edition, Vol. II, edited by Hans Neurath, Academic Press, New York. 1964. 840 pages, illustrated and indexed. Price $26.

The writer had an opportunity to review Vol. I of this three-volume series, and there is no question that Vol. II continues the excellent and authoritative treatment initiated with the publication of Vol. I.

This book contains five rather extensive chapters. The first (chapter 7), "The Conformation of Polypeptide Chains in Proteins," and the last (Chapter 11), "X-Ray Analysis and Protein Structure," are concerned primarily with structural features of proteins in solution and in the solid state. Chapter 7 probably suffers from overemphasis on optical methods; that is entirely understandable because recent progress in the field of conformation of polypeptides in solution has been sparked by the technique of optical rotatory dispersion. On the other hand, the chapter by Dickerson on X-ray analysis is a comprehensive treatment of X-ray analysis as it pertains to proteins. Although the reader of Chapter 11 will be confronted with Fourier transformations and Bessel functions, this chapter still contains much descriptive material which should be of value to the uninitiated. Dickerson justifiably emphasizes the importance of the contributions of Astbury, who is well known to cosmetic chemists for his pioneering studies of keratin, and the importance of the technique of isomorphic replacement, which has borne fruit in the elucidation of the structure of globular proteins. In the text, Dickerson clearly subscribes to the 9 + 2 arrangement of α-helices in keratin without reference to the cogent argument by Sikorski against this arrangement.

A third chapter (Chapter 10), "Polyaminoacids as Protein Models," is actually also concerned with the structure and configuration of protein-like materials. This chapter is primarily descriptive and touches on many features and techniques which have been used to study proteins and protein-like materials.

The shortest chapter (Chapter 9), "Interacting Protein Systems," is concerned with interactions between two proteins. The rates of formation, the classification of products, and techniques for the study of these products are discussed.

The outstanding chapter of this volume is probably Chapter 8, contributed by Steinhardt and Beychok, "Interactions of Proteins with Hydrogen Ions and Other Small Ions and Molecules." A careful study of this chapter will be most rewarding to all who are concerned with proteins in one form or another. The many features of this chapter include a clear and concise introduction to the definition of pH and to the thermodynamics of the chemical potential. In addition, this chapter includes discussions of techniques and descriptive data on the combinations of small ions and of unionized molecules with proteins.

This volume is not designed for casual reading but represents a massive and comprehensive document, the value of which to the practicing chemist and biologist will become apparent only after careful study. In addition, this volume should serve as an authoritative reference and introduction to specific areas of protein chemistry and protein physics. —MARTIN M. RIEGER—Warner-Lambert Research Institute.

HANDBOOK OF CHEMISTRY AND PHYSICS, 45th Edition, edited by Robert C. Weast, The Chemical Rubber Co., Cleveland, Ohio. 1964. Price $15.

The Rubber Handbook in its old format has been a trusted and steady companion of chemists in all laboratories for many years. It is likely, therefore, that the 45th Edition in its revised format will carry on the established tradition. Aside from the change in size, the enlargement of the tables of Organic and Inorganic Compounds and the extensive Description of the Elements are particularly noteworthy. Most chemists will also welcome the inclusion of the rules for nomenclature as adopted by the I.U.P.A.C.

It is understandable that the publishers of a work of this type and size (about 1500 pages) are anxious to utilize existing plates in order to be able to produce the volume at a reasonable cost. As a result, the mathematical tables and many other tabulations appear in the size which has for many years been the trademark of the Rubber Handbook.

This reviewer spotted one error in the Index which gives the ionization constant of amino acids on page D76 whereas, in fact, this information appears on page C667. The reviewer was also disappointed to find that the section on definitions and formulas has not been revised and that such items as the Mossbauer effect and the principle of parity are not covered.

Despite these minor defects, there can be no doubt that the Handbook of Chemistry and Physics is one of the soundest investments that any chemist can make.—M. M. RIEGER—Warner-Lambert Research Institute.

ENZYME NOMENCLATURE, Recommendations 1964 of the International Union of Biochemistry, Elsevier Publishing Co., Amsterdam-London-New York. 1964. 219 pages indexed. Price $2.50.

This volume presents the recommendations of the International Union of Biochemistry on the nomenclature and classification of enzymes together with their units and symbols of enzyme kinetics which were approved during the meeting of the International Union in Rome in February, 1964. The booklet contains seven relatively short chapters and a list of lengthy appendices. The chapters are devoted to a discussion of enzyme units, rules for nomenclature, symbols of enzyme kinetics, and classification of specific enzyme groups. The major portion of this volume is devoted to a list of enzymes (Appendix E). This tabulation includes the accepted systematic name, the trivial name, specificity, and the catalyzed reaction for each enzyme. This effort to correct and up-date the earlier report (1961) of the International Commission on Enzymes will be appreciated by biochemists throughout the world.

It is obvious that this volume is not meant for pleasure reading but that its main purpose is to serve as a handy reference and useful dictionary.—M. M. RIEGER—Warner-Lambert Research Institute.

SURVEY OF PROGRESS IN CHEMISTRY edited by Arthur F. Scott, Vol. I (1963) and Vol. II (1964), Academic Press, New York, N. Y. Price $7.95 each.

A recent ad for one of the well-known national magazines questioned whether the education of a college graduate stops when he is handed a piece of the skin of a dead sheep. It appears that the editor of this series hopes that these and succeeding volumes will answer this rhetorical question. In the preface to Vol. I the editor states that the primary target of the survey is the chemistry teacher, but he also hopes that the survey will meet the needs of many other chemists who would like to keep abreast of what is happening in chemistry outside of their own field of specialization. Generally, it appears that these aims of the survey are met, and it is hoped that the reception of these volumes will warrant the continuance of this series.

It appears rather futile to list the thirteen chapters of these two volumes, all of which have been contributed by experts in their field. The topics appear to be selected at random. Each is covered fairly thoroughly, stressing especially developments during the last ten years, although basic information gathered during earlier years is also discussed. It is obvious that most chapters are directed at readers who already have some knowledge of the subject under discussion. The emphasis on progress during the period since most working chemists have left school makes this survey particularly welcome. In contrast to the Annual Reports published by the Chemical Society in London, the treatment of the various subjects is more thorough and detailed and requires little or no reference to the original literature, although each chapter is provided with numerous literature references.

It is unlikely that any specialist will find much of immediate interest in these two volumes. However, those interested in chemistry and those who would like to keep up with the progress of chemistry in areas outside of their own narrow field of interest will find these volumes most valuable. Their cost is reasonable, and leisurely reading of many of these chapters should prove rewarding and will bring up-to-date information to the reader.

It is hoped that the editor will continue to publish this survey without deviating from the existing format and keep the chapters relatively short and readable.—M. M. RIEGER —Warner-Lambert Research Institute.

PROGRESS IN INDUSTRIAL MICROBIOLOGY, Volume 5, edited by D. J. D. Hockenhull, Gorden & Breach, Science Publishers. 1964. 326 pages. Price $13.50.

This is the fifth annual edition covering various subjects pertaining to applied bacteriology. Each of the seven chapters is written by experts from England, Japan and the United States.

The cosmetic chemist or bacteri-

ologist is not too deeply concerned with the discussions in the chapters titled "The Selection, Improvement and Preservation of Micro-organisms," "The Microbial Production of Amino Acids" and "The Bio-Chemistry of Vitamin B_{12} Fermentation." The first article mentioned above concerns itself with selecting new organisms for producing antibiotics, their genetics, breeding technics and strain improvement. The second and third articles are self-descriptive and, while the end-products may—some time or other—be useful in the cosmetic industry, the bacteriological manufacturing procedures are not.

Aside from the physical, chemical and antimicrobial activity of Bacitracin, there is little of value to the cosmetic chemist in the chapter, "Bacitracin, Its Manufacture and Uses." In this respect, however, the information given under "clinical applications" and "miscellaneous uses" may give some cosmetic chemists ideas for new products.

The chapter, "Preparation of Alkaloids by Saprophytic Culture of Ergot Fungi," while interesting from a scientific standpoint, has no practical use for the cosmetic chemist. However, the chapters, "Modern Trends in Steam Sterilization" and "Microbiological Aspects of Radiation Sterilization," are of considerable interest to both the cosmetic chemist and the bacteriologist. The former chapter discusses all facets of steam sterilization, even to the design of various types of autoclaves, testing autoclaves, cooling autoclave contents after sterilization, automatic operation of sterilizers, faults of autoclave operation and overseas practice in sterilization. Most faulty autoclave operations have been traced to faulty installation, lack of adequate and correct maintenance and faulty instructions to the operators.

The field of radiation sterilization is relatively new and foreign to most chemists and bacteriologists. The chapter on this subject will help to overcome this situation as it is an excellent dissertation on theory and practical implications. Applications include the sterilization of vaccines, antisera, biological tissues, pharmaceuticals, plastic items, rubber gloves, sutures, etc.

Each chapter in this book is followed by pages of references extremely useful to those who wish to pursue these topics more fully.—JAMES H. BAKER—Gar-Baker Laboratories, Inc.

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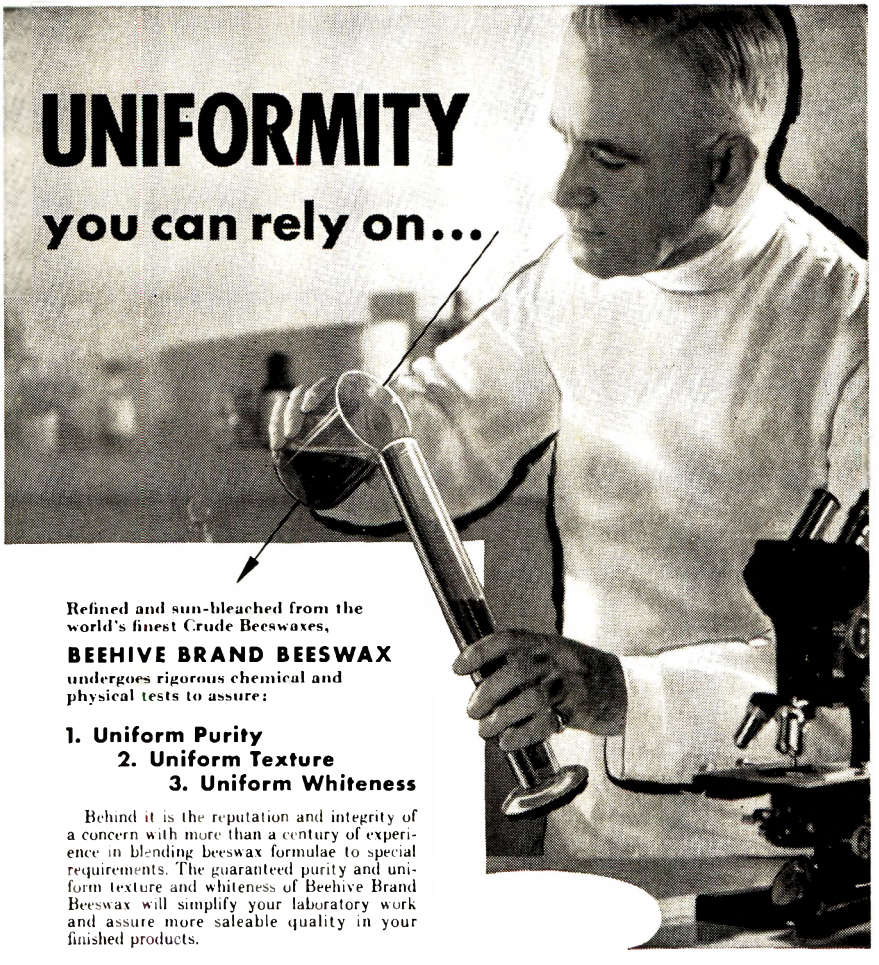

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