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Journal of the Society of Cosmetic Chemists

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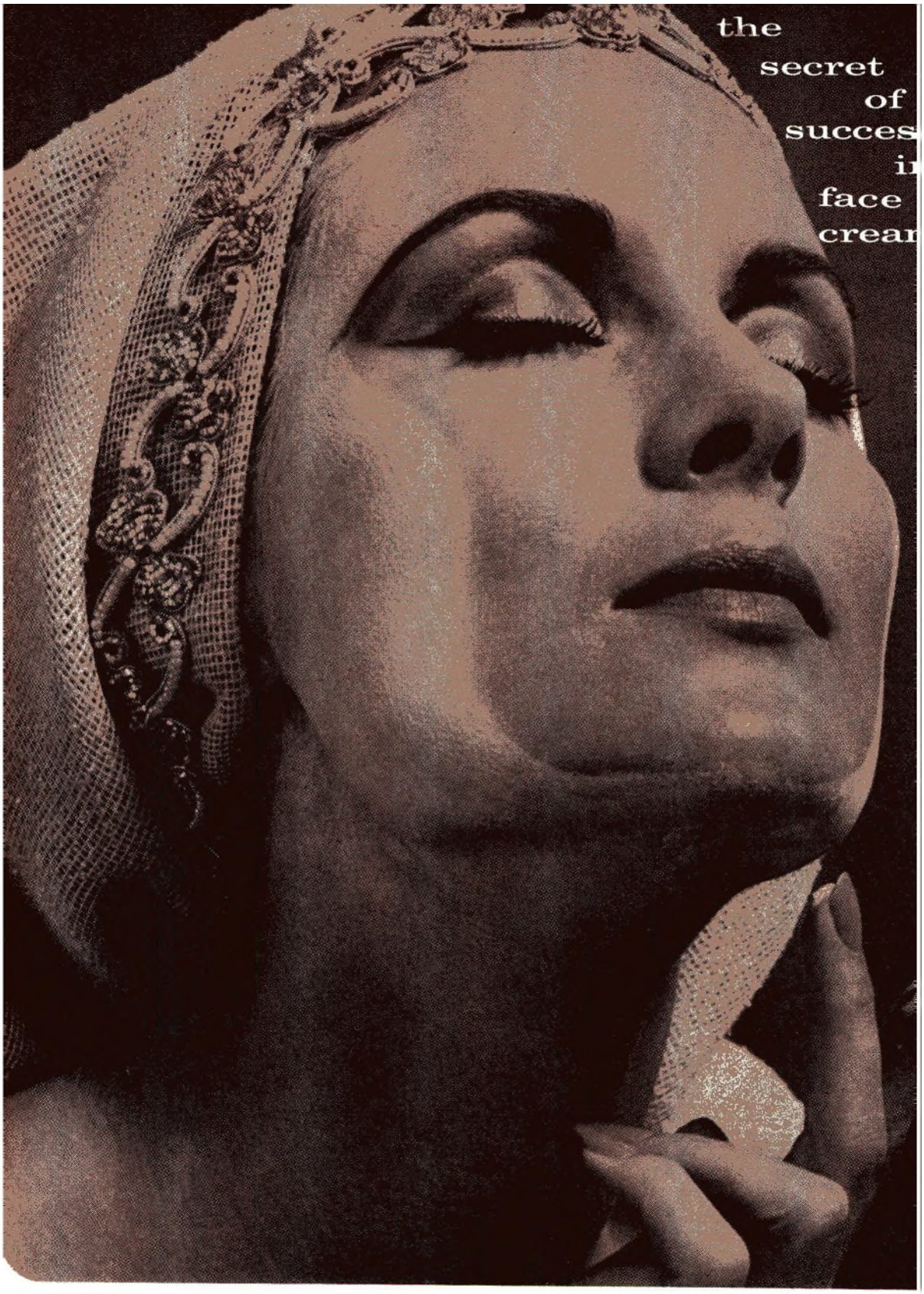

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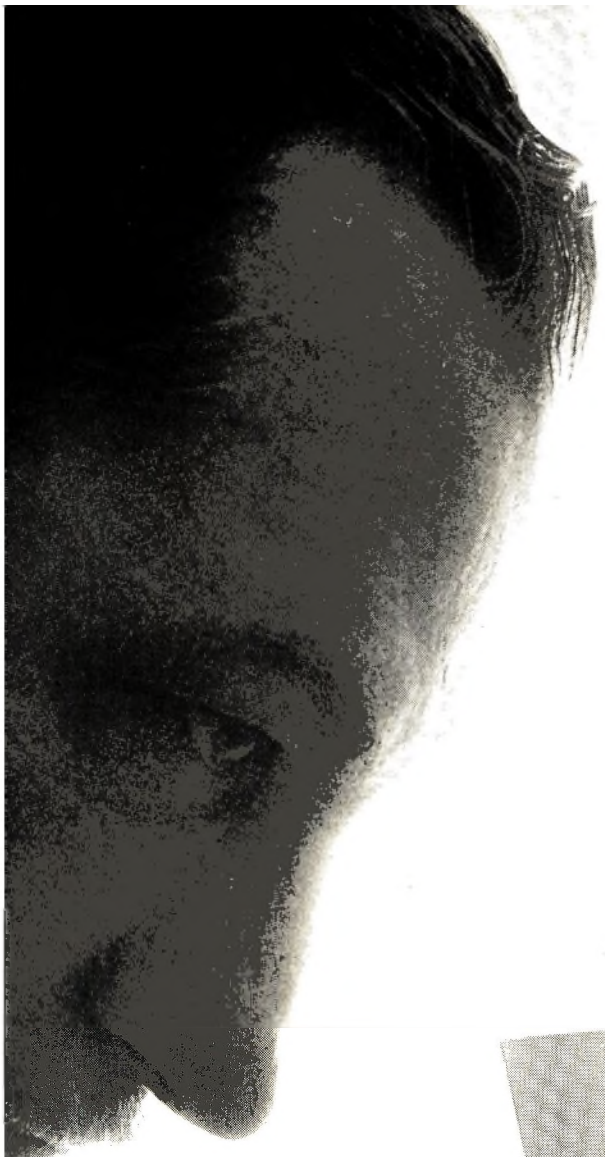

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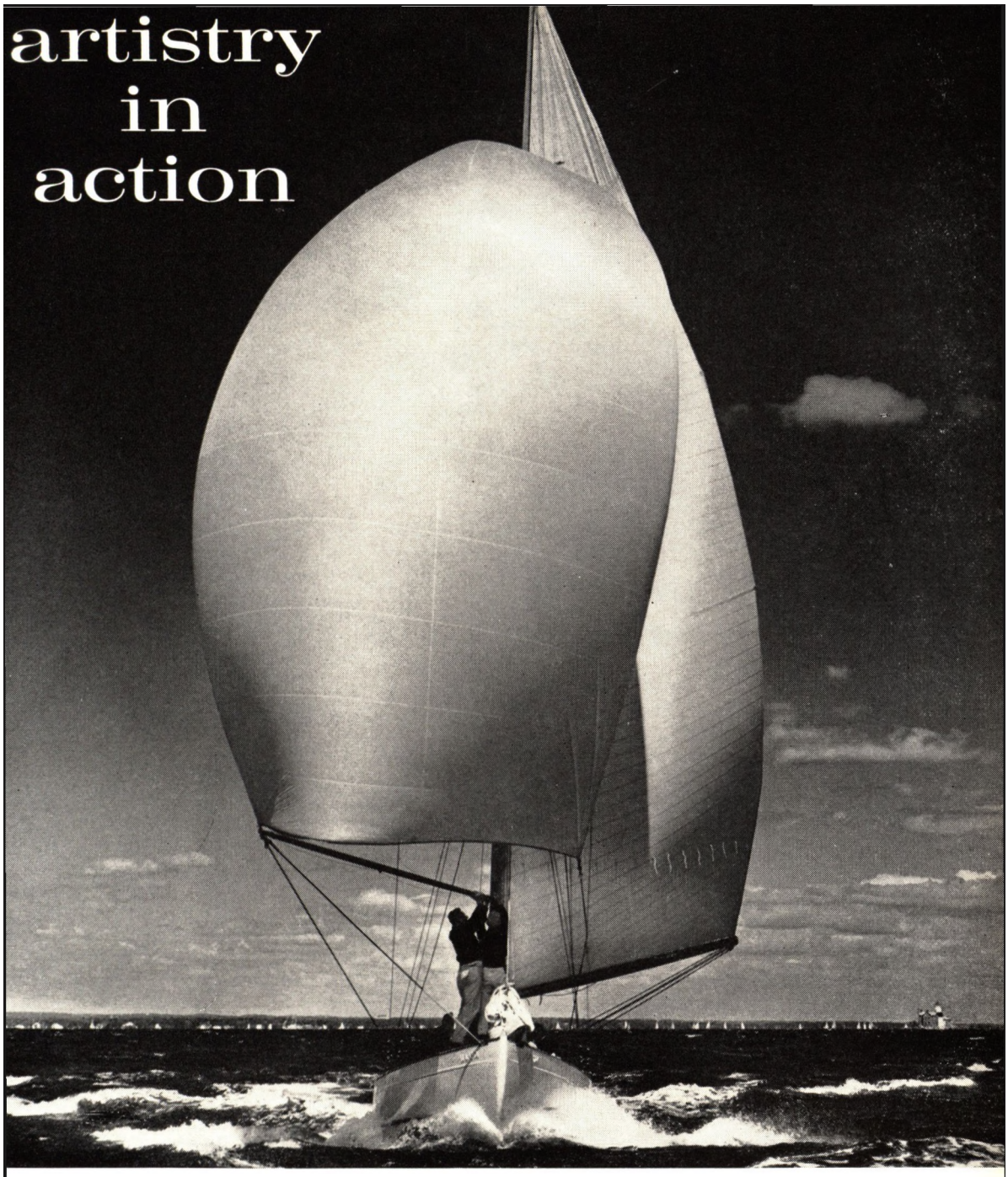

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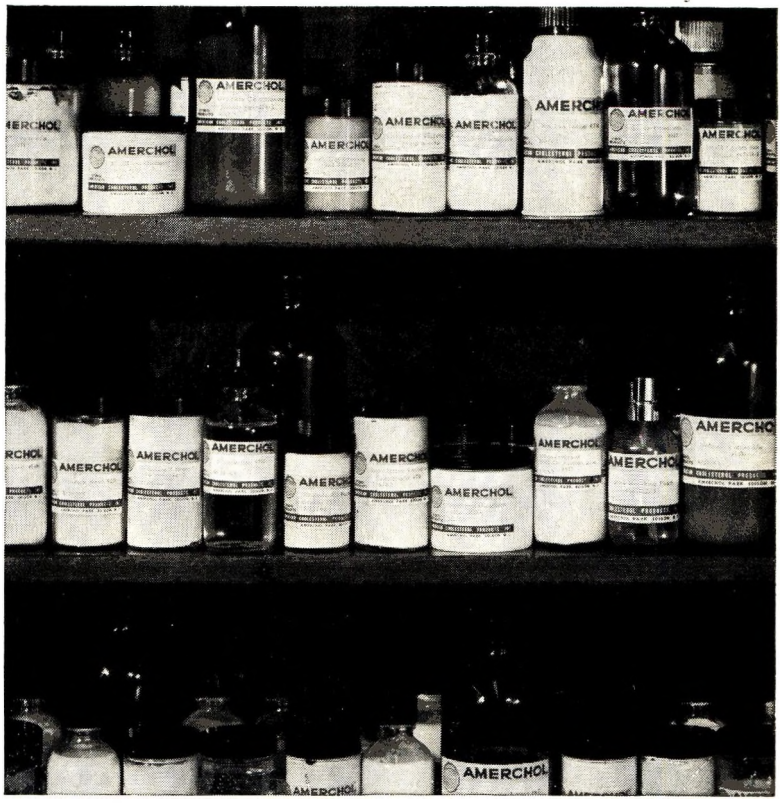

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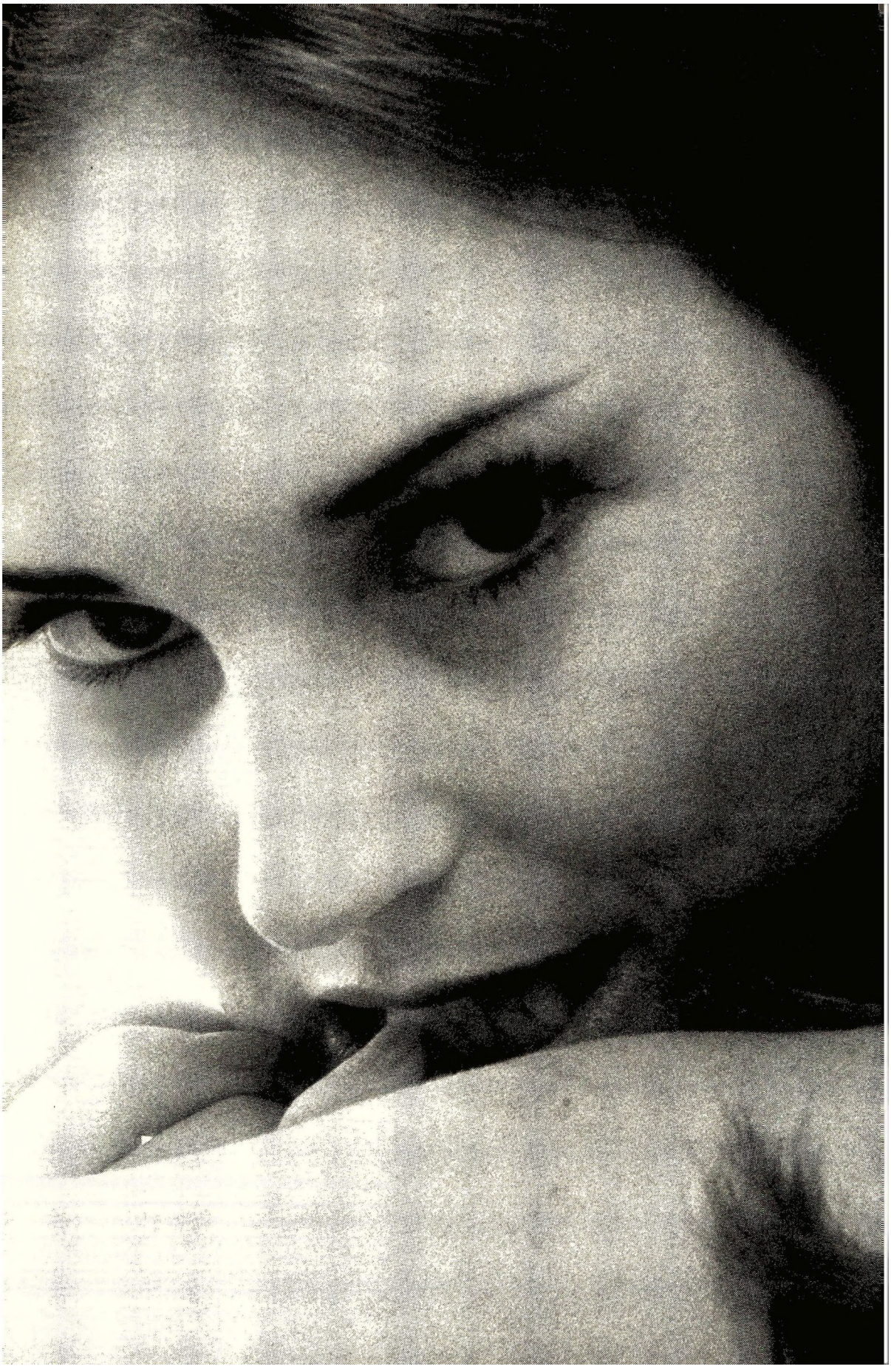

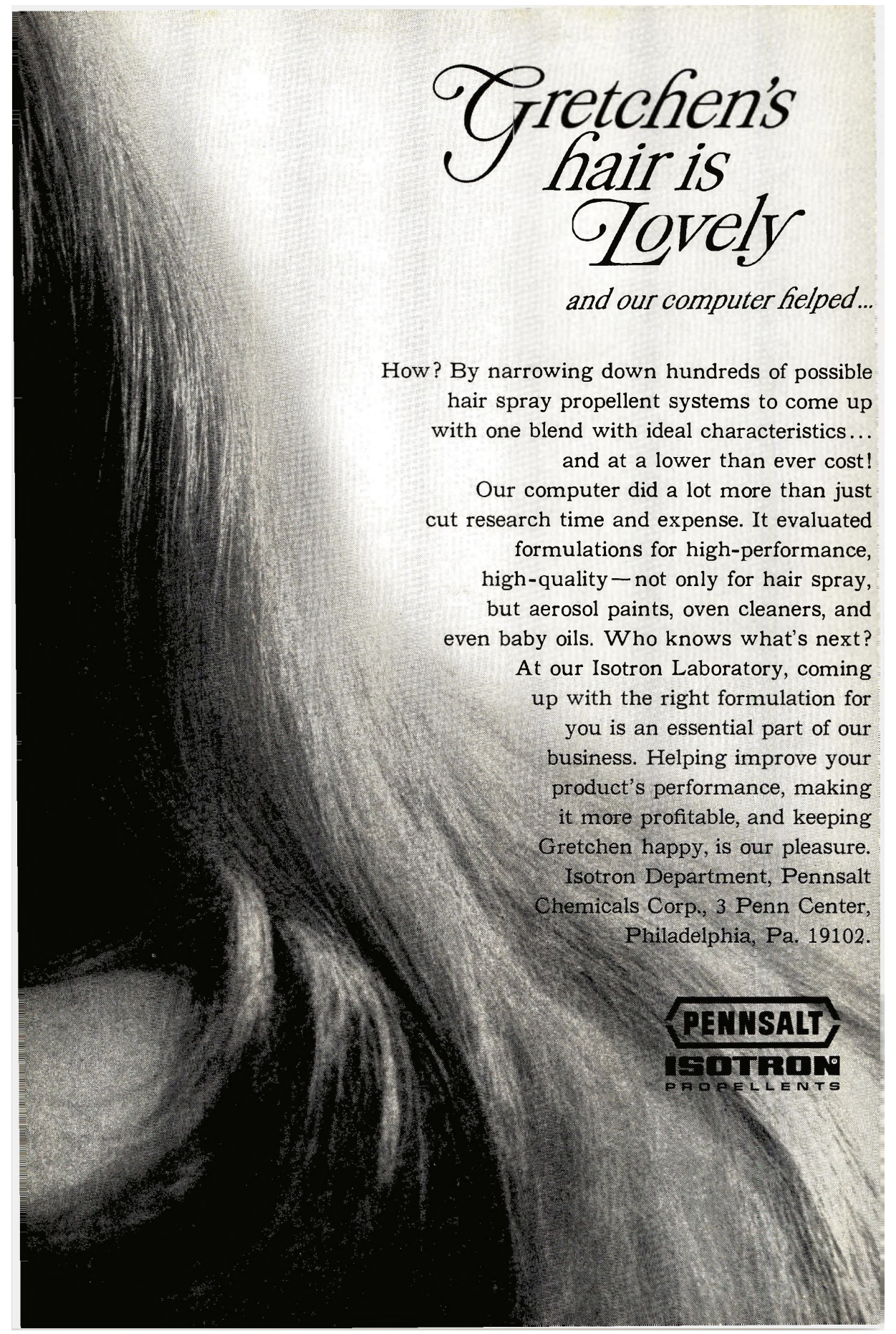
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SYNOPSES FOR CARD INDEXES

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

Product stability: Prognostication, placement, parameters—Part II: Lloyd Kennon. *Journal of the Society of Cosmetic Chemists* **17,** 313 (1966)

Synopsis—Chemical kinetics provides the basic principles which can help study of the deterioration of pharmaceutical and cosmetic products. Principles of kinetics, which could be used to predict long-term stability of finished formulations, are reviewed, and techniques are described which can be used in programming stability studies. Finally, those properties of emulsions, suspensions, and solids are discussed which are amenable to measurement and can be used as parameters for establishing and predicting deterioration of finished consumer products.

The use of instrumentation in cosmetic color control: Hugh R. Davidson. *Journal of the Society of Cosmetic Chemists* **17,** 329 (1966).

Synopsis—For many years color measurements have been used in laboratories for the evaluation of color differences. Up until the last few years, however, they were usually employed only for qualitative evaluation in production. During recent years new measuring instruments, techniques, and computers have been developed in order to permit routine use in color production problems. These new techniques are described. Some of the basic theory is reviewed, but the emphasis is on the practical application. The use of a colorant mixture computer is described in detail.

Use of human subjects for product evaluation: An evaluation of antibacterial soap bars: John A. Kooistra, Elmer A. Bannan, and R. Owen Carter. *Journal of the Society of Cosmetic Chemists* **17,** 343 (1966).

Synopsis—It is shown that *in vitro* microbiological testing of antibacterial-containing soaps is frequently unreliable and is influenced by the strain of the organisms used. On the other hand, *in vivo* testing under laboratory controlled or consumer testing conditions can be used to establish the degerming efficacy of sanitizing soap bars. Several techniques for conducting such tests are described.

Cyclic salicylanilides as antibacterial agents: Winthrop E. Lange and Jon C. Anderson. *Journal of the Society of Cosmetic Chemists* **17,** 355 (1966).

Synposis—A number of halogen, trifluoromethyl, and sulfur-containing salicylanilides along with cyclic derivatives of these same compounds were prepared for evaluation as antibacterial agents. The effects of structure modification on activity were shown by a densitometric minimum inhibitory concentration technique. The trifluoromethyl-substituted salicylanilides and their cyclic derivatives were found to be the most potent antibacterial agents.

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Analytical

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Analysis of Natural Fat Triglycerides. IV. Symposium. *J. Am. Oil Chemists' Soc.* **42,** 1029–53 (December 1965).

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Particle Size Analysis. Barnes, M., *Mfg. Chemist* **37,** 47–50 (January 1966).

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* Prepared by Joseph H. Kratochvil and Joseph L. Rosenstreich.

An Ion-Exchange Column Chromatographic Method for the Separation and Quantitative Analysis of Neutral Monosaccharides. Walborg, E. F., Jr., and Christensson, L., *Anal. Biochem.* **13,** 177–85 (November 1965).

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Society of Cosmetic Chemists Advisory Committee

Left to right: Mr. H. J. Amsterdam, Mr. William H. Mueller, and Mr. Sabbat J. Strianse

Mr. William H. Mueller, Associate Director of Research of The Toni Company, President of the Society of Cosmetic Chemists, recently presented plaques to two past presidents of the organization in appreciation for their seven years of service on the Advisory Committee of the Society. The recipients were: Mr. H. J. Amsterdam, Vice-President of Cosmetic Research & Development of International Flavors and Fragrances, Inc., and Mr. Sabbat J. Strianse, Executive Director of Yardley and Company, Ltd., and Director of Research of Yardley Research Laboratories.

NEW ENGLAND CHAPTER OFFICERS FOR 1966

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Winder, Robert R., Yardley of London, Union Blvd., Totowa, N. J.
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J. Soc. Cosmetic Chemists, **17**, 307–311(1966)

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Correctly prepared journal references are shown below; please note all punctuation marks:

(1) Gaul, L. E., and Underwood, G. B., Relation of dew point and barometric pressure to chapping of normal skin, J. Invest. Dermatol., 19, 9–19 (July 1952).

(2) Jones, S. T., U. S. Patent 3,123,456 (September 15, 1963).

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(3) Rothman, S., Physiology and Biochemistry of the Skin, The University of Chicago Press, Chicago, Ill., 1954, pp 494–560.

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(4) Gershon, S. D., et al., Permanent Waving, in Sagarin, E., Cosmetics: Science and Technology, Interscience Publishers, New York, N. Y., 1957, pp. 585–587.

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Society of Cosmetic Chemists 1966 Meetings

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

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

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Product Stability: Prognostication, Placement, Parameters—Part II*

LLOYD KENNON, Ph.D.†

Synopsis—Chemical kinetics provides the basic principles which can help study of the deterioration of pharmaceutical and cosmetic products. Principles of kinetics, which could be used to predict long-term stability of finished formulations, are reviewed, and techniques are described which can be used in programming stability studies. Finally, those properties of emulsions, suspensions, and solids are discussed which are amenable to measurement and can be used as parameters for establishing and predicting deterioration of finished consumer products.

Parameters

The purpose of this section will be to present a discussion of parameters, that is, physical properties of a formulation which can be measured and to which numerical values can be given. Furthermore, we will wish to examine parameters which change with the stress of time alone or after other challenging stresses (either with or without elapsed time) are applied to the formulations under study. Therefore, we will not be interested in all of the general stresses which are used to generate product development laboratory reports but rather in those which will cause changes in *parameters which can be plotted kinetically* so that we may try to predict stability by noting how the parameters are changed by the stresses. These are not always easy to find as some stresses, temperature and time included, will destroy the products, and we will be up against a limitation not unlike the Heisenberg Uncertainty Principle. Also, we want stresses and parameters which can be used on products *per*

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se and not just on components, because the latter usually act differently when separated from their system.

This section will then be a partial and eclectic guide to the literature; it will be designed to suggest that what has been done in certain areas of the all-encompassing fields of pharmacy and chemistry may also be applicable to cosmetic product development work. It appears that not a great deal of work has been done on physical stability testing techniques; this observation was also noted by Lachman (17) in an article in which he discussed various aspects of physical and chemical stability testing. Some of the work cited here will illustrate the measurement of parameters the usefulness of which may be of a low order. However, it is hoped that these items will be of sufficient general interest so that the reader will consider them as pertinent as the author does because they touch upon this discussion. The references will be divided into categories based on general formulation type. Besides this categorization, no particular order will be followed; some references will describe theory, some suggest stresses or techniques, and others will illustrate kinetic plots.

Emulsions

Becher (18) pointed out in a discussion of spreading, HLB, and emulsion stability that a correlation exists between these factors. To effect correlation he used the concept of spreading coefficient, i.e., a parameter obtained by measurement of the surface (cohesion) and interfacial (adhesion) tensions involved. These are related to the mutual spreading properties of the two phases. When the work of adhesion is greater than the work of cohesion, spreading takes place (positive spreading coefficient); this is generally bad for stability. However, the author points out that too negative a spreading coefficient is not necessarily ideal because a balance between this coefficient and a low interfacial tension is needed.

An early discussion of the theoretical considerations concerning the electric double layer and its influence on emulsion stability is that of Cheesman and King (19). They especially noted the influence of electrolyte content on stability. Experimentally they followed stability by observing the separation represented by the rate of movement of the separation meniscus in a tube.

Higuchi and Misra (20) raised some very interesting points concerning emulsion stability. Usually we think of physical emulsion degradation as taking place only through coalescence. These investigators

studied the physical degradation of emulsions *via* molecular diffusion, i.e., not contact-caused coalescence but a no-contact process in which one droplet grows while another dissolves. The process which predominates could be determined by whether forces exist which hold the droplets apart (latter) or by whether there is a very low degree of solubility of internal phase in the external phase (former).

Although no quantitative predictive technique was realized, Tober and Autian (21) pointed out that a straight-line relationship existed when time to reach 10% v/v sedimentation was plotted against the relative centrifugal force applied to an emulsion. This force is a function of the square of the revolutions per minute and the rotating radius. Stress of the formulation followed by such measurements might lead to predictive techniques.

Singleton and co-workers (22) were interested in making emulsions which would be stable to the heat of the sterilizing autoclave. They did not plot their data kinetically but did describe two of the stresses they used. One was steam autoclaving for 20 minutes at 121 °C; if the particle size became greater than 7μ, the formula was considered unstable. The other was a mechanical shock treatment in which 50 ml. of emulsion in a 100 ml. bottle was shaken horizontally 250 times per minute. Similarly, the emulsion was considered unstable if the particle sizes were greater than 7μ in less than one hour of shaking.

Harrison and James (23) in a study of O/W emulsions showed the existence of relationships between the electrical resistance and the concentration of the dispersed phase. Although they did not use their data kinetically in a stability study, it is obvious that this might be done.

King and Mukherjee (24, 25), in an attempt to create a quantitative criterion of emulsion stability, defined the stability coefficient of an emulsion as the reciprocal of the rate of change of the interfacial area per unit area of existing emulsion interface. They also obtained curves of interest by plotting either the per cent of total number of droplets or the per cent of total oil volume against droplet diameter. They observed that, although the maximum number of droplets are of a certain size, the greatest volume of oil is in drops of a different diameter. These investigators also plotted specific interfacial area *vs.* time. The slopes, although they observed changes such that they used the early and steeper slopes, were equated to rates of decrease of area per unit area of interface. The latter quantity is known, and the rate of decrease could then be used to compare emulsions. Incidentally, one other parameter they suggested was a half-break time, or the time it takes to reach half of the initial

specific area. The change in slopes mentioned, due to two rates of coalescence, an early fast one and a later slower one, indicated the existence of an exponential relationship. Levius and Drommond (26) also illustrated the heat stressing of emulsions after which the usual methods of size frequency analyses and calculations of interfacial areas were applied.

In our discussion of size and interfacial area relationships, it aids perspective and is interesting to note that Ross (27), in a discussion of emulsions, pointed out that 2-μ droplets have a surface area of about 30,000 cm.^{2}/cc. whereas 3-μ droplets have an area of 20,000 cm.^{2}/cc.

Higuchi, Okada, and Lemberger (28) studied O/W emulsions in which the droplets were about 1μ and the system relatively monodispersed. They use a Coulter counter to determine the distribution of the various sizes of droplet aggregates. Thus, they were able both to count and size the aggregates as a function of time. They developed a method which quantitatively studied aggregation directly so that the aggregation would not have to be deduced from creaming or sedimentation rates. Hence, emulsions could be stored and the size distribution after various times be determined; the distribution could indicate if larger aggregates are being formed. This would be a warning as larger aggregates would indicate an increased chance of coalescence in emulsions or caking in suspensions.

Of interest is the early paper of Berkman (29) who studied emulsion stability by a size distribution method utilizing a projection microscope to measure globule size; 1500 to 2000 measurements were made per curve. She found that changes in distribution were related to time and that the pattern of progression was followed and agreed with data taken on emulsions five years old.

Lotzkar and Maclay (30) obtained interfacial areas by a size frequency analysis employing photomicrographs. They were able to plot the log of the specific surface area of the dispersed phase *vs.* time and obtained straight line plots. They noted that the degree of dispersion and the initial viscosity (although viscosity will hinder creaming) did not always increase stability.

Mullins and Becker (31, 32) investigated factors influencing the stability of O/W emulsions using high pressure homogenization. They also studied the feasibility of adjusting the density of the phases by the addition of brominated oils and the possibility of making the internal phase thixotropic by adding wax. They used a size-frequency method of analysis and showed that specific interfacial area increases with increased

homogenization pressure. The presence of internal wax did not help, although the density adjustment did in some cases. The emulsions were stored at room temperature and 45°C to hasten deterioration, after which a microscope was used to measure the diameters of 900 to 1000 globules to obtain the size frequency classification. The globules were divided into size groups, and the midpoints of these groups were considered to be the average diameters. Considering the globules to be spheres, the volume and area were calculated, and these were then used to obtain the area per unit volume or the specific interfacial area. When plotted against time this parameter, of course, showed a decrease.

Sherman (33) pointed out the influence of the kinetics of globular coagulation or aggregation (precursors to coalescence) on the rheological properties of aging emulsions. His goal was to predict viscosity changes over long aging periods. Since the changes depend on globule size, he made emulsions of various sizes to get a picture of what would happen in the future. He noted that this technique may be better than centrifugation or high temperature storage, even though such stresses may produce an increase in average globule size. He interrelated many measurements and developed a parameter, called the inhomogeneity factor, which increases with time. The factor essentially converted data obtained by measuring 2000 globules to a distribution parameter which accounts for globule number, size, and area. Also as a further and more detailed comparison, Sherman calculated the average distance between globules which is also related to the average diameter. Finally, this average distance of separation was related to viscosity data, which means that globule diameter is related to viscosity. Thus, if globule diameter increases and has an effect on viscosity, both old and fresh emulsions of the same globule size should have the same viscosity. Sherman found that when relative viscosity was plotted against the distance separating the globules, or against time, the data from both new and old emulsions could be superimposed; thus viscosity changes over long aging periods could be predicted.

This discussion of finished emulsions and coalescence is somewhat reminiscent of the coalescence time test of Cockbain and McRoberts (34). In essence, their test requires that the emulsion be put together in two parts: the oil phase is layered over the water phase after which an oil drop is introduced from the bottom underneath the water. After the drop rises to the interface, one checks to see how long it takes for it to coalesce. Of course, the longer this time, the more stable the completed emulsion is considered to be.

Lloyd (35) related the per cent reflectance of color and the surface average diameter obtained microscopically in a study of the change in distribution pattern of the globule sizes of O/W emulsions. A straight line plot resulted when the log per cent reflectance was plotted against the log surface average diameter. The latter quantity, which of course is inversely related to interfacial area, is then also capable of relating stability to reflectance. We note also that interfacial area simulates a concentration factor as it can be expressed as interfacial area per unit volume of oil. Lloyd found that a plot of log diameter *vs.* time gave a curve which rose steeply in first order fashion and then reached a plateau which indicated limiting of the coalescence.

Menczel, Rabinovitz, and Madjor (36) used a selectively soluble dye (soluble in only one of the phases as used for the differentiation of emulsion types) to color their test emulsions with an exact amount of such a dye. They then developed a colorimetric method to determine volumes of separated internal phase at various times. The rate of this separation is then equated to the rate of de-emulsification. They employed a dye soluble in the internal phase and used a separatory funnel to collect the separated portion from the emulsion bulk. The internal phase was thus collected at various times from a series of preparations; its volume was determined colorimetrically by measuring the dye concentration with a photoelectric colorimeter. The volumes were converted to per cent separation. A straight line log-log relationship was found by plotting the log of the per cent separation *vs.* log time. A family of lines resulted; the position of any particular line of the family then is an indication of the stability rank of the particular emulsion.

Vold and Groot (37) developed an ultracentrifugal method to determine emulsion stability. They investigated the utility of an ultracentrifuge which permitted observation of the emulsion while it was being rotated. When the per cent of oil separated was plotted *vs.* the time of centrifugation, a plateau curve was obtained. It was noted that the separation rate was very rapid at first, then slower and more-or-less constant while 20 to 60% of the oil separated, and finally, the rate was slow. Naturally, increased speeds caused higher rates of oil separation. Centrifugation speeds up to 56,100 r.p.m. were employed. Garrett (38) also studied the use of the ultracentrifuge in predicting pharmaceutical emulsion stability, especially as it pertains to oil flotation or creaming. A linear graph resulted when flotation rate was plotted *vs.* the square of the centrifuge revolutions per minute. The flotation rate is represented by the slope of the line which results when the log distance of

emulsion-water boundary from the rotor center is plotted *vs.* time for each revolutions per minute.

An earlier example of the use of centrifuge studies is the work of Merrill (39). This investigator studied the mechanical stability of O/W and W/O emulsions by measuring the rate of separation of internal phases when the emulsions were subjected to a constant centrifugal force. The quantitative index of stability used was the reciprocal of the initial rate of separation at a certain centrifugal speed. Plots of per cent oil separated *vs.* time of centrifuging were linear.

Suspensions and Selected Solutions

Martin (40) discussed the physical-chemical principles involved in suspensions. Such parameters as sedimentation height were noted; here one determines the ratio of the ultimate height of the sediment to the initial height of the suspended material. Naturally, the larger this fraction is the better is suspendability. He also noted the applicability of electrophoresis which employed a microelectrophoresis apparatus. Such instrumentation could measure migration velocity with respect to the surface electric charge or the familiar zeta potential, which has units of viscosity times electrophoretic mobility, or, more familiarly, voltage.

Stanko and DeKay (41) evaluated suspensions by electrokinetic methods. Since pH, sedimentation rate, and viscosity would not necessarily indicate everything that is happening in the system, it was felt that the electrokinetic properties, that is, the zeta potential and critical potential (zeta potential at which flocculation occurs) would be illuminating. The zeta potential was obtained in a microelectrophoresis apparatus from which the rate of movement of particles could be obtained. These workers plotted the weight of sediment *vs.* time and obtained gently curving lines. Although no kinetic plots were made, it was shown that the zeta potential changes upon the addition of additives and that it is related to stability.

Haines and Martin (42, 43) studied some formulation factors which influence the stability of suspensions. They correlated zeta potential to the measure of visually observed caking. The zeta potential was determined by microscopic electrophoresis, and it was found that certain zeta potentials produced more stable suspensions because flocculation was controlled.

Foernzler, Martin, and Banker (44) studied the effect of thixotropy on suspension stability. They obtained straight line graphs by plotting the sedimentation velocity in a centrifuge at a particular RPM in ml./

min. against the reciprocal of the thixotropic area. The sedimentation velocity was obtained by plotting the sedimentation volume *vs.* time. The thixotropic area is the area of the hysteresis loop formed when the viscosity of a non-Newtonian liquid is taken continuously over a range of stress-strains and back; the area was measured with a planimeter on the plots of rate of shear *vs.* shearing stress. The authors thus attempted to predict physical stability by the rheologic evaluation of thixotropy. Incidentally, Wood (45) used these workers' data to show that a similar or better correlation exists if the reciprocal of the yield value is plotted against the sedimentation velocity.

Wood, Catacalos, and Lieberman (46) studied aging magnesium aluminum silicate suspensions. They found new, interesting, logarithmic, atypical kinetic relationships involving the time and temperature of storage and shear rate and shear stress. Plots of log shear stress *vs.* log shear rate produced a family of straight lines for a particular storage temperature in which the slopes decreased with sample age, although the older samples' lines "started higher," i.e., required more stress to get the same shear rate as the younger. Thus plots of log apparent viscosity *vs.* log age were linear for each particular shear rate. These workers also pointed out that plots of log apparent viscosity at a single shear rate *vs.* either log age at a particular temperature or $1/T$ at a particular age were linear; the latter indicates that viscosity build-up follows an Arrhenius type of relationship. Thus plots of log age to attain a given viscosity at a particular shear rate *vs.* $1/T$ were also linear. For practical purposes it is noted that work such as this illustrates that clay and gum hydration is not attained instantaneously—it is part of the aging process and is not necessarily completed even by the stress a formulation undergoes in a manufacturing procedure.

Garrett and Carper (47) studied the color stability of a multisulfa suspension after it was exposed to accelerated temperature storage conditions. They followed the UV absorbance of the supernatant liquid after the suspension was centrifuged. They observed that the absorbance *vs.* time at the different temperatures provided straight lines from which they could calculate first order rate constants. Their data also fit an Arrhenius plot from which they could predict after a four-week study the rate of deterioration of the color after one year at room temperature.

Levy (48) studied the stability of the viscosity of various molecular weight sodium carboxymethylcelluloses and sodium alginates in aqueous solutions stored at an elevated temperature. When the log per cent of the initial viscosity was plotted aginst time, a linear first order plot

resulted from which a viscosity half-life could be calculated. This half-life decreased with increasing molecular weight.

In a study of the viscosity of suspending agents, Joslin and Sperandio (49) noted straight line (and some curved) relationships obtained by plotting viscosity *vs.* time. Not surprisingly, some experiments resulted in a family of lines with respect to different storage temperatures and also, some samples became thicker with time, some thinner. Storage at elevated temperatures accelerated the particular changes.

Zacek (50) illustrated the use of ductility as a response variable of pharmaceutical suspensions. In essence, he suggests placing the suspension between two plates which are then pulled apart vertically. A thread between the plates forms, and the distance at which it breaks is measured.

With respect to stressing suspensions, the freeze-thaw cycle technique is very applicable. This treatment facilitates particle growth and may indicate the probable future state of affairs after long storage at room temperature.

Schwarz and Levy (51) studied the viscosity of sodium alginate solutions after freezing and thawing. They showed that the viscosity increased upon such treatment. They also demonstrated that excessively long shearing lowered the viscosity, although the freeze-thaw cycle caused all to have the same viscosity regardless of the initial. They also pointed out, however, that an increased rate of shearing may give a permanent loss of viscosity, as will higher temperatures, because of the degradation of polymer chains.

Head and Lauter (52) used an ultrasonic generator to study the depolymerization of natural polymers. It is known that such insonation will depolymerize, but it also can facilitate gum hydration. They showed through viscosity measurements that the molecular weight decreased and that a straight line plot resulted when the molecular weight was plotted against the duration of irradiation. Carrageenan, agar, locust bean gum, and methylcellulose all degraded first order; gum tragacanth degraded according to zero order kinetics; karaya and acacia were not degradable by their method.

Semi-solids and Solids

Urbanyi and co-workers (53) measured the changes in reflectance of colored tablets with a reflectometer attachment on a spectrophotometer, choosing the best wavelength for observation. Reflectance was compared to a standard. They used this technique to determine the in-

fluence of light of 45 and 550 foot-candles intensity. Absorbance was plotted against time, and some first order rate constants were obtained, although the plots were not ideal as the lines were segmented. Naturally, the constants increased at the higher light intensities. Lachman *et al.* (54) in additional work which was part of an extensive study of tablet dyes checked the fading of the corresponding lakes. From absorbance and time data, they obtained first order rate constants and showed that the lakes studied had poorer photostability than the dyes.

Carstensen and collaborators (55) employed photometric reflectance to observe the appearance of tablets and powders stored at elevated temperatures. Their data provided them with both zero order and first order rate constants which were amenable to Arrhenius plot treatment.

Everhard and Goodhart (56) studied the fading of dyes in tablets. Their aim was to quantitate the time-intensity relationships involved in the storage of a single tablet dye at various concentrations (0.015 to 0.060%). The tablets were stored under 655 foot-candles, fluorescent lights at 80 foot-candles, fluorescent light and amber glass at 11 foot-candles, and under incandescent light of 50 foot-candles. They pointed out that others had plotted log of log $1/R$ *vs.* time where R represented the fraction of light reflected at a specified wavelength. These workers pointed out that the previous work inferred that log $1/R$ was proportional to concentration but that this was not so because different rate constants were obtained for different dye concentrations. Thus, they noted the need for an equation to relate reflectance to concentration and also a need to bring light intensity into the kinetic picture. They showed that a parameter called ϑ_t was proportional to concentration where: $\vartheta_t = (1 - R_t)^2/2R_t$ and R_t = the measured reflectance at the minimum wavelength in a reflectance-wavelength curve. Then, considering fading to be proportional to time and intensity, a straight line resulted when ϑ_t was plotted *vs.* $I \times t$ in foot-candle hours.

McKeehan and Christian (57) studied the color stability of a bentonite base cream with an integrating sphere reflectometer, which is useful for the study of opaque solids and semisolids. When the creams were stored at various elevated temperatures, they were able to plot reflectance (relative to magnesium carbonate) *vs.* time and obtain straight lines. They were also able to construct Arrhenius plots to permit prediction of the time when the color would be unsatisfactory. They also proposed use of the technique for the study of coated tablets, powders, and granulations.

It is possible that dilatometry can serve to monitor changes such as hidden phase transitions (formation of solid solutions or immiscible phases) and polymorphic transformations in semisolids such as pastes and ointments. Such techniques were employed by Ravin and Higuchi (58) in part of a series of studies on the melting behaviors of some fats and waxes of pharmaceutical importance. The procedures are reproducible and entail determining the specific volume of a system as a function of temperature. Although it was not done by these investigators, it is possible that samples would be stressed in the usual accelerated storage tests, after which dilatometric studies would be performed. Possibly, a plot of specific volume at a certain temperature *vs.* time of storage would give data from which predictions could be made. The utility of a different type of dilatometry, constant temperature dilatometry, has been pointed out by Mahler (59). In this technique the aim is to avoid the effect of temperature on polymorphic changes. Thus, the material is kept at room temperature in something akin to a mercury densitometer. The volume change, either an increase or a decrease, is then followed by recording the displacement of mercury in a connected capillary tube as a function of time. When the per cent change in volume is plotted against time, the curves plateau out, either upward or downward depending on whether a volume increase or decrease takes place. From the early part of these curves, which are essentially hyperbolas, one can calculate the time required to complete the variations in volume which are due to polymorphic transformations. Thus, the time to make observations for surface defects which are caused by such transformations can be predicted for such products as lipsticks, eyebrow pencils, suppositories, etc.

Reese, Chong, and Swintosky (60) studied lipid raw materials *via* photomicrography. They were able to demonstrate that some changes (crystal transformations, growth, cracks) occurred during aging at room and accelerated temperatures. Certainly, the integrity of lipid materials affects the quality of creams and ointments, and it is possible that, even though it may be difficult to quantitate, this camera-microscope technique could be used to detect incipient graininess in ointments. Also, it may be possible to observe the solid phase of suspensions this way.

Maclay, Shepherd, and Lotzkar (61), in a study of pectin in medicated pastes and ointments, measured the viscosity and pH of such products stored at various temperatures. Although the pH gradually decreased, the viscosity was relatively stable. However, they could demonstrate by analytical techniques a slow demethoxylation of the pectin.

Szepesy (62) studied the consistency of ointment bases by obtaining penetrometer readings at 6°, 25°, 35°, and 45°C initially and after storage of the ointments.

An interesting property which permits evaluation of lotions, creams, and ointments is that of tack. Wood and Lapham (63) described an instrument, the tackmeter, which permits the evaluation of tack of such products, both after they are dried on plates or after application to the skin. The tackmeter described is essentially a balance assembly which permits determination of a withdrawal weight and time of break to separate a flat surface of the device from the skin. Wood, Giles, and Catacalos (64) also described a revised tackmeter in which forces were recorded by a strain gauge instead of by weights.

Borchardt and Daniels (65) studied the application of differential thermal analysis to reaction kinetics. Although they used solutions, one could visualize the application of the technique to semisolids such as pastes, ointments, and lipsticks. The method detects the net heat of reaction as the temperature of the system is raised. The difference in temperature of the reacting solution and a reference solution obtained while both are heated is plotted against time (temperature). The equations enable one to calculate the heat of reaction from the area under the curve and the reaction rate constant at any particular temperature from the slope and height of the curve at the particular temperature. The heat of activation and the order of reaction are then obtained from plots of log k *vs.* $1/T$.

Pohle, Gregory, and Taylor (66) described work on the comparison of analytical techniques for predicting the relative stability of fats and oils to oxidation. Most of these stability testing methods attempt to force the oxidation of the fat or oil, after which either oxygen absorption is measured or organoleptic or chemical methods are used to monitor the degradation of the product. As part of a series of studies on the oxidation of emulsified and solubilized oils, Carless and Nixon (67) studied the oxidation of methyl linoleate. They measured oxygen uptake manometrically in a Warburg apparatus, in addition to the more usual checking of peroxide values. Somewhat along this line, Ravin, Kennon, and Swintosky (68) studied an oxidative reaction by measuring oxygen uptake in a Warburg respirometer; the oxygen uptake was monitored while the system was stressed with a sun lamp. They showed that oxygen uptake was linear with time and that it stopped when the light was turned off. Briefly continuing these comments on oxidation, we note that Reese and Guth (69) irradiated calamine lotions with UV, sunlight, and both

incandescent and fluorescent lamps and checked peroxide formation iodometrically; it is known that aqueous zinc oxide may produce hydrogen peroxide. They showed that the source of the zinc oxide and other ingredients influences the peroxide generation by the zinc oxide. They found that the increase in hydrogen peroxide concentration with time was not linear.

In conclusion, we may note the fact that Bartels (70) has pointed out the possible utility of various types of quantitative microscopy in solving problems connected with cosmetic R&D work. In fact, speaking of parameters, he suggests that parameters which indicate a good correlation to the effect we wish to observe be created, regardless of whether they are common to the present scientific literature or not.

Conclusion

Early theoreticians and experimentalists have given us a heritage, part of which we recognize as the principles of what today is known as physical chemistry. The seemingly necessary—or at least ever-present—pace of today has stimulated workers in the pharmaceutical industry to use some of this inheritance, namely that portion specifically pertinent to the present discussion, i.e., basic chemical kinetic concepts. The promise of tomorrow seems to be that even more of these techniques will be found to be applicable to product development efforts in the cosmetic industry. The thoughts expressed here concerning further progress in this direction have taken the form of suggestions based on a discussion of possible quantitative ways which monitor the changes formulations go through upon storage. Of course, more data are required before firm conclusions can be reached, but if work along this line is implemented, many exciting areas may be opened up for study. Certainly, our aim must be to do everything we can to enhance our knowledge of the "systems" we call "products."

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The Use of Instrumentation in Cosmetic Color Control

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Synopsis—For many years color measurements have been used in laboratories for the evaluation of color differences. Up until the last few years, however, they were usually employed only for qualitative evaluation in production. During recent years new measuring instruments, techniques, and computers have been developed in order to permit routine use in color production problems. These new techniques are described. Some of the basic theory is reviewed, but the emphasis is on the practical application. The use of a colorant mixture computer is described in detail.

Introduction

Within the plastics, textiles, and paints fields the use of instrumentation for color control has become much greater during the past few years. Over 150 installations in these fields have proved to be successful in reducing costs, improving quality, and increasing production. The interest in instrumentation is now spreading into the cosmetic industry. The problems which will be encountered here are similar to those in other fields, and there is every reason to suppose that instrumentation for cosmetic color control will prove as beneficial as it has in other industries.

Among the first of these instrumental systems, and by now the most widely used, is that employing the Davidson and Hemmendinger Colorant Mixture Computer (COMIC). It is the purpose of this paper to describe briefly the theory behind this system and to discuss some applications in cosmetics.

* Davidson and Hemmendinger, Inc., Easton, Pa.

Color Theory

The primary specification of the color of a given sample is based on the spectrophotometric curve. The solid line in Fig. 1 is the spectrophotometric curve of a beige powder in the form of pressed cake. Plotted horizontally on the graph is the wavelength of light. The vertical dimension of the graph represents the relative amount of light reflected by the sample. Figure 1, for example, shows that less than 30% of the blue light is reflected and about 60% of the red light is reflected. The exact reflectance of the sample for any wavelength of light may be read directly from the curve.

The spectrophotometric curve of a colored product has several useful properties. If two samples have identical spectrophotometric curves, one will be a color match for the other, assuming no differences between them in texture or gloss. Furthermore, these two samples will appear to be a match regardless of what light is used for illumination and regardless of whether the observer has normal color vision. Unfortunately, however, the converse is not true. One cannot assume that if two samples are a color match under one particular illumination they have identical spectrophotometric curves and will match in all illuminants. The samples may be metameric; that is, they may match under one illuminant but not under another. In this case the spectrophotometric curves will not be identical. This problem of metamerism is responsible for many of the color matching problems in industry.

Another important property of the spectrophotometric curve of a mixture of pigments is that it exhibits the spectral characteristics of the individual pigments used in the mix. The color represented by Fig. 1, for example, was made with an iron oxide red, Mapico®* yellow, ultramarine blue, and white (titanium dioxide). The spectrophotometric curves of these pigments are shown in Figs. 2 and 3. It should be noted that the characteristic valleys which appear in the curves of the mixtures of the colored pigments with white also show up in Fig. 1, i.e., when all three pigments are used in the mixture. The Mapico yellow shows a characteristic dip in the 400 to 450 nm range in both Figs. 1 and 3. The red shows the same slope in the 550 and 580 nm range in both Figs. 1 and 2. The characteristic slope of the ultramarine blue in the region 650 to 700 nm shown in Fig. 3 is repeated in Fig. 1, although somewhat obscured by the red and yellow. Because these pigment characteristics are retained in mixtures, appropriate pigments may be

* Mapico is a trade name of Columbian Carbon Co., Trenton, N. J.

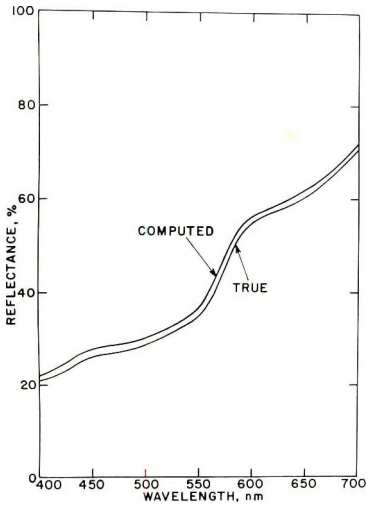

Figure 1. Spectrophotometric curves of a pressed cake sample ("True") containing red iron oxide, Mapico yellow, ultramarine blue, and titanium dioxide and the predicted curve ("computed") based on the known pigment quantities

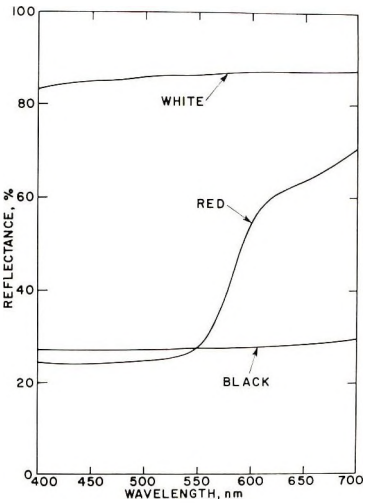

Figure 2. Spectrophotometric curves of pressed cake samples containing white only, a mixture of 1% red iron oxide and 99% white, and a mixture of 1% black and 99% white

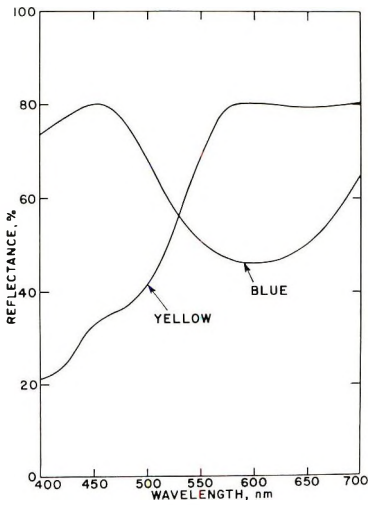

Figure 3. Spectrophotometric curves of pressed cake samples containing 1% ultramarine blue and 99% white, and 1% Mapico yellow and 99% white

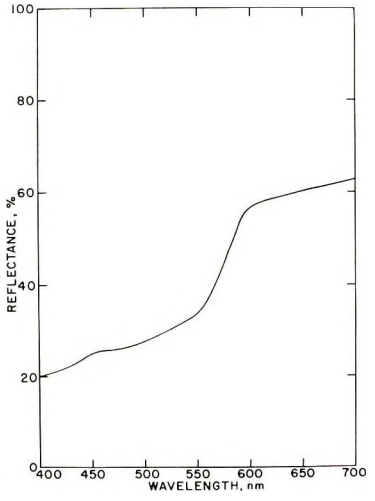

Figure 4. Spectrophotometric curve of a pressed cake sample containing Mapico yellow, red iron oxide, black and titanium dioxide

chosen on the basis of the spectrophotometric curve. For example, if an attempt were made to match the color shown in Fig. 1 with a powder containing black in place of ultramarine blue, a curve similar to that shown in Fig. 4 would have been obtained. Notice that the flat curve of the black as shown in Fig. 2 produces a flatter curve than does the blue in region 600 to 700 nm. Thus if black rather than blue had been used, only a metameric match to the powder the curve of which is shown in Fig. 1 would have been obtained. It might be a satisfactory match under one light but not under another. On the basis of the spectrophotometric curve, then one should attempt to match the sample with blue rather than black as the dulling component. Although the choice of pigments required to match the color of Fig. 1 is fairly obvious from the curve shapes, the choice is frequently not this apparent and becomes clear only after quantitative calculations have been made.

Determination of the amount of pigment required is usually based on the Kubelka-Munk (1) theory. The basic relationship may be expressed in the following equation, where K/S is the ratio of the coefficient of absorption to the coefficient of scatter and R is the reflectance.

$$K/S = \frac{(1 - R)^2}{2R} \qquad 1$$

This equation is true for an opaque material at any given wavelength of light. It may be assumed that the value K/S is proportional to the per cent concentration of colored pigment relative to white pigment in the material and that the K/S value in a mixture of pigments is a simple additive function of the K/S values for the individual pigments. These assumptions are described mathematically in equation 2 and are valid except for colors in which the white pigment content is very low.

$$K/S_M = C_A K/S_A + C_B K/S_B + C_C K/S_C + K/S_W \qquad 2$$

The values K/S_A, K/S_B, and K/S_C are values for unit concentration of pigments A, B, and C in white and C_A, C_B, and C_C are the concentrations of the pigments in the mixture. K/S_W is the value for the white alone; K/S_M is the value for the mixture. All of the K/S values, of course, are for the same wavelength. By the use of this equation, the K/S value for a specified mixture of pigments can be predicted, providing the K/S values for the individual pigments at unit concentration are known. Equation 1 may then be used to compute the predicted reflectance at the

TABLE I

Pigment Calibrations

	White		1% Red Oxide			1% Mapico Yellow			1% Ultramarine Blue		
	R	K/S	R	K/S_M	K/S_R	R	K/S_M	K/S_Y	R	K/S_M	K/S_B
400	83.0	0.017	24.1	1.195	1.178	20.5	1.542	1.525	73.5	0.048	0.031
450	84.8	0.014	24.1	1.195	1.181	33.1	0.676	0.662	79.9	0.025	0.011
500	85.7	0.012	24.8	1.140	1.128	42.0	0.401	0.389	68.3	0.074	0.062
550	86.2	0.011	27.8	0.938	0.927	71.0	0.059	0.048	50.6	0.241	0.230
600	86.9	0.010	54.5	0.190	0.180	80.1	0.025	0.015	46.0	0.317	0.307
650	87.0	0.010	63.5	0.105	0.095	79.5	0.026	0.016	50.4	0.244	0.234
700	87.4	0.009	70.5	0.062	0.053	81.5	0.021	0.012	65.5	0.091	0.082

same wavelength,* and this prediction may be made for a large number of wavelengths. It will be apparent, therefore, that by means of equations 1 and 2 the spectrophotometric curve of any mixture of pigments may be predicted, providing the values for the individual pigments are known. An example will help to clarify the method.

Table I lists the reflectances of 1% concentrations of red oxide, Mapico yellow, and ultramarine blue in titanium dioxide. These values were taken directly from the spectrophotometric curves of the pigments shown in Figs. 2 and 3 and are given for the wavelengths shown. In the next column to the right of that giving the reflectance, the corresponding K/S values are given. These values are for the mixture of 1% colored pigment and 99% white and are equivalent to the K/S_M value given by equation 2 for one colored pigment plus white. In order to get the K/S values for the pigment alone, the K/S values for white, which are also given in the table, are subtracted. This has been done to obtain the "corrected" K/S values in the next column to the right. It is these corrected values labeled K/S_Y, K/S_R, and K/S_B which must be used in equation 2.

Now let us try to predict the reflectance at 500 nm of a mixture of:

Red oxide	0.5%
Mapico yellow	0.5%
Ultramarine blue	0.2%
White	98.8%

Using equation 2 and the values in Table I one finds:

$$K/S_M = 0.5 \times 1.128 + 0.5 \times 0.389 + 0.2 \times 0.62 + 0.012 = 0.782$$

The tables of K/S *vs.* R indicate that a K/S value of 0.782 corresponds to a reflectance of 30.7%. Thus one would predict the reflectance of this mixture to be 30.7% at 500 nm. The actual reflectance of the mixture, labeled "True" in Fig. 1, is 28.6%. Similar calculations can be made at each of the wavelengths for which data are tabulated. This has been done, and the results are plotted in Fig. 1 (labeled "Computed") so that the predicted curve may be compared with the actual curve. It will be noted that the predicted curve is 1½ to 2% higher than the true curve. The two different colors represented by these two curves would not be a sufficiently good match for most cosmetic applica-

* In practice, however, tables of K/S *vs.* R are used rather than calculations in accordance with equation 1. Such a table appears in Ref. 1.

tions, but they would be close enough so that an adjustment, as will be described below, would produce a color which would be an acceptable match to the standard. The error in prediction may be due to a number of causes such as variations in pigment strength, grind, or errors in sample preparation.

The manner in which this spectrophotometric theory is utilized will be described below. For a full understanding of the computer, however, some colorimetric theory will also be required.

The color of a sample may be described in terms of its tristimulus values, X, Y, and Z. If two samples have the same tristimulus values, they will match under the illuminant for which these values were computed even if the spectrophotometric curves are not identical. The tristimulus values may be computed from the spectrophotometric curve by means of equation 3.

$$\begin{aligned} X &= \int E\bar{x}Rd\lambda \\ Y &= \int E\bar{y}Rd\lambda \\ Z &= \int E\bar{z}Rd\lambda \end{aligned} \qquad 3$$

E is the relative distribution of energy in the light source used for viewing the sample, $\bar{x}$, $\bar{y}$, and $\bar{z}$ are values dependent on the characteristics of the human eye, R is the reflectance of the color, λ is the wavelength of light, and the integration is carried out over the entire visible spectrum. All of these values vary with wavelength, and the values for $\bar{x}$, $\bar{y}$, $\bar{z}$, and E have been standardized by the International Commission on Illumination. The computation is usually made either by an automatic computer attached to a recording spectrophotometer or by a combination of filters and photocells in a colorimeter. Similarly, the difference in color between two samples having differences of ΔR in their spectrophotometric curves is given by equation 4.

$$\begin{aligned} \Delta X &= \int E\bar{x}\Delta Rd\lambda \\ \Delta Y &= \int E\bar{y}\Delta Rd\lambda \\ \Delta Z &= \int E\bar{z}\Delta Rd\lambda \end{aligned} \qquad 4$$

If one can predict the spectrophotometric curve of a sample having a given pigment formula by means of equations 1 and 2, then one can also predict the color by use of equation 3 and the predicted reflectance values. It will be apparent that one can also predict the color difference between two samples having known pigment composition by use of equations 1, 2, and 4. Although this technique predicts color from known pigment formulas, the method gives, at least in theory, a means

of predicting a pigment formula to match a given color. If one tries to match the color specified in Fig. 1, for example, one can guess at a formula, compute the curve, and compare it with Fig. 1. On the basis of the differences between the predicted and desired curves, one can estimate a new formula and try again. By successive trials, one can eventually arrive at a pigment formula for which the predicted curve would be identical with the desired curve; and this formula would then be the predicted formula for matching the sample. The difficulty of course, lies in the amount of time required to make these calculations. It is at this point that computers can solve the problem.

Practical Use of the Colorant Mixture Computer

The Davidson and Hemmendinger Colorant Mixture Computer, COMIC, is a high-speed computer designed specifically for solving equations equivalent to equations 2 and 4. The control panel is shown in Fig. 5. Values of K/S for the individual pigments to be used in match-

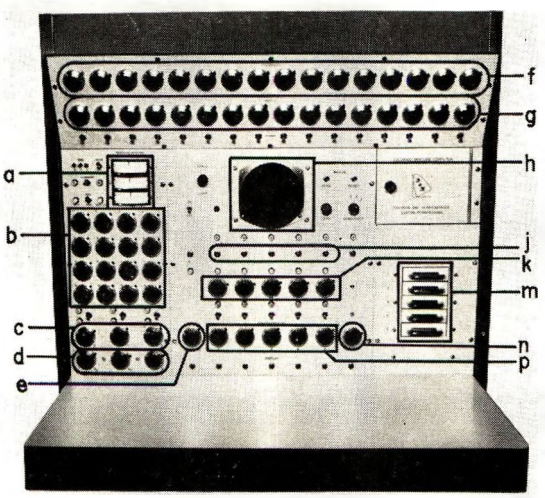

Figure 5. Control panel of the Colorant Mixture Computer

ing are adjusted in individual plug-in boxes, five of which can be placed into the computer at one time. These plug-in boxes are labeled "*m*" in the figure and are often referred to as "primaries." Usually a box is available to represent each of the pigments which might be considered for a match, and these boxes are set up before the computer is used for any matching problems. These K/S values are derived from the spectrophotometric curves of mixtures of the colored pigment and white similar to those shown in Figs. 2, 3, and 4. Since the computer can

handle the values for 16 wavelengths, the values chosen are usually at 20 nm intervals from 400–700 nm.

The standard to be matched is measured at the 16 wavelengths, and the K/S values are set on the dials labeled "f" in Fig. 5. On the oscilloscope tube "h" 16 dots appear. These dots represent the spectrophotometric curve of the standard to be matched. The operator first chooses the pigments he wishes to try and inserts the plug-in boxes representing them. If by adjusting the concentration dials "p" he can bring all of the dots down to the zero line, he has chosen correct pigments for a nonmetameric match, and the required amounts will appear on the concentration dials. The position of the dots is actually a display of the difference between the solution of 16 equations similar to equation 2 and the K/S values for the standard. When the dots are all on the zero line, the differences between the predicted K/S values and the desired K/S values are zero, indicating that the spectrophotometric curve predicted for the mixture of pigments is the same as that of the standard to be matched.

Figure 6 presents an example of use of the computer for matching a color similar to that shown in Fig. 1. The pattern of dots on the oscilloscope tube are shown for each step in the match. Figure 6a shows the position of the dots representing the spectrophotometric curve of the standard to be matched. Since this is an absorption curve, it is inverted with respect to the normal spectrophotometric curve shown in Fig. 1. On the basis of this curve the operator decides which pigments to try. He chooses a red oxide, Mapico yellow, and ultramarine blue; he plugs the boxes representing these pigments into the computer and adjusts the concentration dials to bring the dots onto the straight line. Several steps in this process are illustrated in Figs. 6b, c, and d. Addition of the blue by means of the appropriate concentration dial adjusts the dots in the long wavelength region of the spectrum; addition of the red brings the dots in the middle of the spectrum down to the line; and, finally, addition of yellow straightens out the line in the short wavelength region at the left. In this case, the operator chose the proper pigments, and therefore all of the dots can be brought to the zero line. This indicates that a nonmetameric match to the standard may be made with the pigments chosen, and the required amounts of each pigment are shown on the concentration dials. However, if the operator had chosen to dull the color with a black instead of the blue, he would have found it impossible to bring all of the dots down to the zero line. In other words, no values of concentration could have been found which would permit

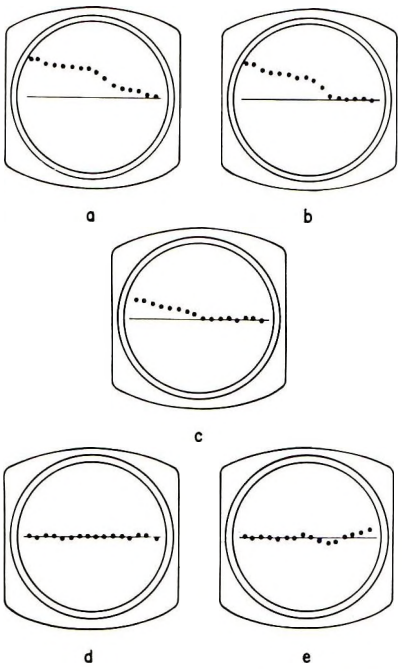

Figure 6. Appearance of the COMIC oscilloscope tube during various stages of solving a matching problem

a solution of 16 equations of the form of equation 2 so that all 16 predicted K/S_M values were equal to the K/S values of the standard to be matched. The appearance of the line of dots would have been similar to that shown in Fig. 6e. If this situation arose, the operator would select a different set of pigments and repeat the operation until an appropriate combination had been selected.

The first trial formula will not, of course, produce a perfect match to the standard. The size of the color difference will depend upon many factors, including the accuracy of the calibration of the primaries, the degree of control over the dispersion of the pigments, and the degree to which the equation truly represents the process. Color differences of from three to eight MacAdam (2, 3) units can be expected on the first trial. Although in most cases a mismatch of this magnitude would be larger than could be tolerated, it is sufficiently small so that computed adjustments will produce an acceptable match after one or two corrections.

Adjustments to the first trial may be made either spectrophotometrically or colorimetrically. If a spectrophotometric correction is to be

made, the reflectance values of the trial sample are converted to K/S values and placed on the dials labeled "*g*" in Fig. 5. The values for the standard are, as before, placed on the dials labeled "*f*." The dots on the cathode ray tube take up positions representing the differences in K/S values between the standard and the trial. Appropriate pigments are then added to, or subtracted from, the formula by means of the concentration dials and polarity switches, labeled "*j*" in Fig. 5, until the dots are all on the zero line. The formula adjustments are then read from the concentration dials, and the signs of the adjustments are given by the polarity switch positions.

Color adjustments may be made more rapidly and in most cases more accurately on the basis of tristimulus values if the color adjustment is small. The differences in tristimulus values (ΔX, ΔY, and ΔZ) between the standard and sample are obtained from a colorimeter or by computation from the spectrophotometric curves using equations 3 or 4. These values are placed on the computer dials labeled "*c*" in Fig. 5. Sixteen values for the standard are then placed on the dials labeled "*b*." These are known as $dR/d(K/S)$ values (4) and are used to convert the voltage differences in the computer which represent K/S differences into reflectance differences, ΔR, for use in equation 4 with which the predicted values of ΔX, ΔY, and ΔZ are computed for any pigment alteration. Three meters, labeled "*a*," are then nulled by means of the concentration dials and switches to obtain the formula correction. If more than three colored pigments are used, the formula is not unique; that is, many different combinations of pigment ratios will produce a colorimetric match. Only one of these combinations will produce a nonmetameric (or spectrophotomeric) match. In this case, the colorist must reduce the problem to control of three pigments, either by using only three pigments to make his adjustment or by specifying one or more of the pigment ratios.

So far it has been assumed that the operator could find a combination of pigments which would produce a nonmetameric match to the standard. This is not always possible. Perhaps the pigments which will produce a nonmetameric match are not certified or are too expensive. Some other combination must be used, and a metameric match may be required. In this case, the operator will be unable to bring all of the dots down to the zero line. In order to determine the correct formula, he must now place the $dR/d(K/S)$ values for the standard on the dials labeled "*b*" and must set the ΔX, ΔY, ΔZ dials, labeled "*c*," at zero. The K/S values for the standard are as before placed on the dials labeled "*f*." Now the operator lines up the dots on the zero line as nearly

as possible, then makes small changes in the concentration dials, "p," until the three meters labeled "a" indicate zero.

The production control problem is equivalent to adjustment of a trial formula. A sample of the batch being processed is measured, and adjustments to the batch formula are obtained from the computer. In most production problems a colorimetric adjustment is satisfactory if appropriate procedures have been established. When the system is properly set up, adjustments can be obtained in less than ten minutes, including measuring time, and one correction is usually sufficient.

System Operation

Several steps are required to set up and operate the color control system which has been described. Before any matching or control work can be undertaken, the pigments must be calibrated. A mixture of each pigment with white at a known ratio is made and the reflectance measured; these measurements are converted to K/S values and set into the pigment plug-in boxes.

When a standard is to be matched, it is first measured on a spectrophotometer, and the appropriate K/S values are set into COMIC. A tentative choice of pigments is then made, and the corresponding pigment plug-in boxes are inserted into the computer. If the operator is unable to obtain a straight line on the computer oscilloscope by adjusting the concentration dials, he makes a different pigment selection and tries again. When a straight line or the best line possible with available pigments is obtained, the operator reads the pigment formula from the concentration dials. The proposed formula is then made up and compared either visually or instrumentally with the standard. If it is not a sufficiently close color match, the reflectance values of the sample are converted to K/S values and are placed in the COMIC along with the K/S values of the standard to be matched. Alternatively, the difference in tristimulus values along with the appropriate $dR/d(K/S)$ values may be used. A correction of the formula is then obtained. A new formula is made up, and the entire process is repeated until a satisfactory match has been obtained.

Adjustments in a production batch are handled much as are adjustments to a trial formula. Usually tristimulus values of the batch sample are measured and placed in the computer along with the values for the standard. After nulling the three meters, the operator reads from COMIC the adjustment required to bring the batch to the standard.

Application to Cosmetic Problems

The example cited to show the operation of the color control computer is a real one chosen from some of the work which has been done on compressed cakes. There appear to be no difficulties in applying these methods to the color control of powder in this form. The same holds true for liquid make-up, although the best method of preparing a sample must be established. Multilayer draw-downs* have been found to be very effective; on the few problems studied the results were excellent, even with measurements made on the liquid make-up in a glass cell. In the case of lipsticks and nail polishes, there are problems of computation on shades containing very little white, just as in paints or plastics. There is also the problem of establishing a satisfactory method of sample preparation for lipsticks. These problems may make it impractical to apply these methods to the very brilliant shades, but the more pastel shades should not prove difficult. The success of these methods in the control of hair dye has already been established by one manufacturer who has been using them for this purpose for about two years.

Conclusions

On the basis of work done on cosmetic problems, it can be predicted that the use of instruments for color control will be as successful in cosmetics as it has been in paints, plastics, and textiles. Certainly not all color problems will be solved by instrumentation, although a sufficiently large portion will be solved to more than justify the use of these methods. In the future further improvements in both techniques and instruments can be expected, but the general methods described here have been so successful that we may be sure they are here to stay.

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* A Bird Applicator normally used for paint draw-downs was used, but we found it necessary to allow the first coating to dry, then place a second on top of it.

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Use of Human Subjects for Product Evaluation: An Evaluation of Antibacterial Soap Bars

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Synopsis—It is shown that *in vitro* microbiological testing of antibacterial-containing soaps is frequently unreliable and is influenced by the strain of the organisms used. On the other hand, *in vivo* testing under laboratory controlled or consumer testing conditions can be used to establish the degerming efficacy of sanitizing soap bars. Several techniques for conducting such tests are described.

For many years efforts have been made to improve the skin degerming potential of skin cleaning agents by enhancing the inherent antibacterial power of soap through the incorporation of specific antibacterial ingredients. Many antibacterial chemicals were tried. It was not, however, until the introduction of hexachlorophene in the mid-forties that a satisfactory agent was found to achieve this purpose. With the demonstration that skin degerming through the use of specific antibacterials incorporated into soap was feasible, the search for new and better antibacterial agents was intensified.

The apparent simplicity of the degerming process is likely to be misleading. Actually, the suppression of the cutaneous microflora through washing of the skin with surface active agents containing bacteriostatic compounds is a complex process. It involves a number of interactions,

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most of which are understood incompletely at best, among the cutaneous microorganisms, the agent, and the environment. Individual microorganisms of the skin differ greatly among themselves in regard to sensitivity to a given antibacterial agent. Agents differ in their ability to deposit from the washing solution on the stratum corneum and to penetrate into the appendages of the skin. The effect of the matrix and the solubility of the antibacterial agent in the liquid phases of the skin surface influence the degree to which the bacterial population is affected. These factors play a role in determining the extent to which a practical objective is achieved; that is, to decrease the number of skin bacteria that can lead to infection and to axillary and other so-called body odors.

In view of such a multifaceted situation, methodology is obviously critical in evaluating new antibacterial agents and in comparing one material or product with another in regard to degerming efficacy. The purpose of this paper is to discuss some approaches currently used for evaluation of skin degerming efficacy and to highlight their advantages and limitations.

Methodology and Discussion

In Vitro Testing

In vitro procedures, because of their relative simplicity, are widely utilized. In order for an agent to warrant consideration at all as a candidate antibacterial ingredient, obviously it must first have antibacterial activity in the matrix in which it is to be used. *In vitro* procedures can be used for screening purposes to supply such information and thus exclude from further consideration compounds with inadequate activity. By their nature, however, these techniques rely on arbitrary selections of test organisms and exposure conditions. They can give reproducible results; however, extrapolation from *in vitro* data to more complex or practical situations has been found by experience to be unreliable.

Many *in vitro* procedures have been advocated, but the type that is most widely used at the present time involves determination of the minimum inhibitory concentration (MIC).

Part of the problem inherent in basing over-all conclusions regarding degerming efficacy on MIC data is illustrated by the information of Table I. This table presents MIC data comparing two antibacterial soaps against a group of 20 different *Staphylococcus aureus* strains isolated from pyogenic infections. Antibacterial Soap A was a milled bar

containing 2% of a mixture of the antibacterials: 3,5-di- and 3,4′,5-tribromosalicylanilides (BSA), 4,4′-dichloro-3-(trifluoromethyl) carbanilide (TFC), and 3,4,4′-trichlorocarbanilide (TCC). Antibacterial Soap B was a milled bar containing 0.75% 3,4,4′-trichlorocarbanilide (TCC) plus 0.75% hexachlorophene (G-11).

Considerable variation among the organisms in sensitivity to both soap bars was evident. Strain 22 required over four times as much of either soap for complete inhibition of growth as did Strain 32. Overall, the data show that the soaps were similar in regard to bacteriostatic

TABLE I

Minimum Inhibitory Concentration Against *Staphylococcus aureus* Strains

	mg./100 g. of product				
	Antibacterial Soap			Antibacterial Soap	
Strain	A[a]	B[b]	Strain	A	B
26	6	8	32	4	4
20	6	8	34	8	8
19	6	6	35	8	8
21	6	6	36	6	6
22	16	16	37	6	6
24	6	6	38	6	6
27	6	6	39	6	6
29	6	6	23	8	6
30	8	8	25	12	8
31	6	6	28	8	6

[a] Antibacterial additive: 2% mixture of BSA, TFC, and TCC.
[b] Antibacterial additive: 0.75% TCC + 0.75% G-11.

activity. If, however, either Strains 20 or 26 had been chosen as the only test organisms, the conclusion would have been that Soap A was superior to B. Had either Strains 25 or 28 been the only test organisms, Soap B would have been judged superior. With each of these strains, the recorded differences between the soap bars were reproducible, but, if the experiment were to be repeated with another group of strains of this same bacterial species, the results might very well be different.

The problem of interpretation of MIC data in terms of the relative skin degerming effectiveness of two products is further complicated when other species of bacteria are used as test organisms. Data in Table II illustrate this complication. MIC values were obtained for Soaps A and B with a group of 20 strains of *Corynebacterium minutissimum* isolated from toe webs of individuals with erythrasma. Overall, the data show Bar A to be superior to Bar B in control of these strains.

TABLE II

Minimum Inhibitory Concentration Against *Corynebacterium minutissimum* Strains

mg./100 g. of product

Strain	Antibacterial Soap A[a]	Antibacterial Soap B[b]	Strain	Antibacterial Soap A	Antibacterial Soap B
P17-1	8	14	P1-1	11	16
P16-1	8	14	P3-3	11	14
P6-1	8	14	P8-2	16	16
1-2	8	16	2A	14	16
10289	8	11	7A	12	16
3A	8	16	P22-1	16	16
12A	6	8	P7-3	16	16
4R	8	16	P1-4	16	16
8L	8	16	P20-1	16	16
P13-1	11	14	P26-3	14	12

[a] Antibacterial additive: 2% mixture of BSA, TFC, and TCC.
[b] Antibacterial additive: 0.75% TCC + 0.75% G-11.

TABLE III

Skin Degerming Effectiveness of an Antibacterial Bar Soap: Constancy of Results

Handwashing—Fifth Basin—Four Day Regimented Usage

Test Product	Test Date	Mean Bacterial Count Per Liter
Antibacterial soap A[a]	1-9-61	9,000
	4-17-61	17,800
	3-11-63	11,300
	1-27-64	13,100
	3-9-64	13,800
	10-23-64	8,900
	10-26-64	1,900
	11-9-64	11,000
	11-9-64	5,700
Control soap[b]		1,300,000

[a] Antibacterial additive: 2% mixture of BSA, TFC and TCC.
[b] No antibacterial additive.

However, if Strain P26-3 had been selected as the only test organism, Soap B would have been judged superior. Had any of the four strains just above it in the table been used, the bars would have been judged equally effective.

Obviously, decisions regarding relative efficacy of antibacterial products based on MIC data are capricious. Results are too dependent upon the bacterial strains that happen to be chosen for the test. For

this reason alone, MIC data do not offer a means of judiciously selecting any one antibacterial bar soap as being superior. Furthermore, the MIC test completely neglects to take into account the effect of the environment in which the product will be expected to perform its function.

Pillsbury (1), one of the pioneers in the field of skin degerming, stated that he was unable to demonstrate that *in vitro* studies were of value in predicting the antibacterial action of an agent on the skin. The way to determine the degerming effectiveness of a skin degerming product is to measure the reduction in the number of bacteria on the skin of panels of people using the product. Such *in vivo* methods are feasible and, if properly designed and conducted, can give reproducible and precise results.

In Vivo Testing

A reliable method for determining the size of the bacterial flora of the skin following various types of surgical scrub regimens was developed by Price (2). The procedure involved a sequence of standardized handwashings (with brush) and the estimation of the number of bacteria removed after each washing. Variations of the basic Price method have been reported (3–5). For the laboratory evaluation of the skin degerming effectiveness of antibacterial soap bars, a further modification of the basic handwashing method has been developed in this laboratory, which over a period of five years has proved to be a precise and practical investigative tool.

A pool of subjects is maintained by supplying individuals with soap bars containing no added antibacterial agents for their hygiene when they are not participating as members of a handwashing panel. Sufficient time is allowed between participation in different handwashing tests to permit the bacterial flora of the hands of each individual to return to its normal level.

From this pool, test panels of 10 individuals (5 males, 5 females) are drawn as required. During a test, each subject is given a bar of test soap to use at home for all handwashing and bathing and a second bar to keep with him for use during the day. In addition, the panelists wash their hands with the test soap under supervision in the laboratory three times daily according to a prescribed routine. In order to minimize possible extraneous factors, panelists are requested not to expose their hands during the test period to other soap solutions (which might remove the antibacterial compounds from the skin) such as in dishwashing, car

washing, shampooing, etc. Rubber gloves are provided for use by those participating in such activities.

At the beginning of the test on Monday morning, before using the test product, and on the following Friday morning, after exclusive use of the test product for four days, an estimate of the number of bacteria on the skin is made. Four successive standardized handwashings are performed in a stream of warm tap water, using a bar soap containing no antibacterial additives. The fifth handwashing (fifth basin) is performed using the same procedure, except that it is done in a basin containing one liter of sterile distilled water rather than in running tap water. The hands are carefully washed and rinsed into the water in this basin. Aliquot samples of the wash water are immediately taken for bacterial enumeration. Pour plates or filter membrane procedures can be used for enumeration. Raw count data are transformed to logarithms for statistical analysis.

Data presented in Table III show the constancy of counts determined over a three-year period when using this handwashing procedure as the analytical tool. The soap used by the panelists was the bar previously described as antibacterial Soap A containing the 2% mixture of BSA, TFC, and TCC. Nine different panels were subjected to the same four-day testing procedure. The number, 1.3×10^6, was included in the table as a reference figure. This bacterial count was obtained from nonantibacterial soap bar users and is an average based on more than 500 individual fifth basin handwashings.

Data showing the skin degerming effectiveness of various concentrations of the antibacterial ingredient, hexachlorophene, incorporated into a milled soap matrix are presented in Fig. 1. With an increase in concentration of the antibacterial ingredients, a progressive decrease in the mean number of bacteria recovered in the fifth basin was evident.

Figure 2 shows the mean number of bacteria recovered in the fifth basin after use of bar soaps containing as antibacterials the following agents:

2.0% Mercuric iodide
1.0% Hexachlorophene
0.5% 3,4,4′-trichlorocarbanilide plus 0.5% hexachlorophene
0.75% Brominated salicylanilides
1.0% 3,4,4′-trichlorocarbanilide

Considerable difference was evident as to their relative effectiveness in reducing the number of bacteria found on the skin.

The skin degerming effectiveness of Antibacterial Bar A (2% BSA, TFC, and TCC) and that of Antibacterial Bar B (0.75% TCC plus 0.75% G-11) are compared in Fig. 3. Each bar on the graph, the mean number of bacteria recovered in the fifth basin, is representative of a single 9–10 member panel. The data were collected over the same general time period. The mean number of bacteria found after four day's regimented use of Bar A ranged from 1,900 to 11,000 for the individual panels with an over-all mean of 5,700. For Bar B, the range

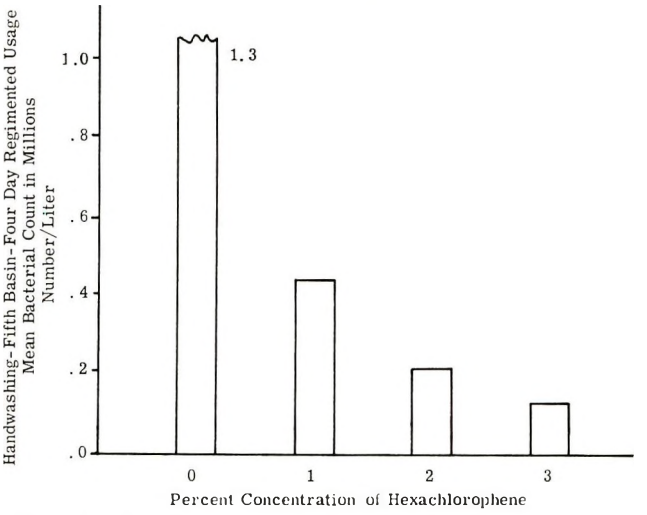

Figure 1. Skin degerming effectiveness of various levels of an antibacterial incorporated into a bar soap matrix

was 48,100 to 91,000 with a mean of 65,100. An analysis of variance showed that the difference between the two bars was statistically significant ($P < 0.01$).

The data presented in Table III and Figs. 1, 2, and 3 demonstrated the capabilities of a refined technique involving usage and handwashing sampling under controlled laboratory conditions. While these results are realistic and valid for the conditions of usage exposure prescribed for the panelists, the ultimate test is to determine degerming effects resulting from normal consumer usage.

For normal consumer usage studies, large panels of housewives are employed. Each subject is given unidentified bars (different shapes, colors, etc.) of the test soap to use at home for all handwashing and bathing. No other restrictions with regard to either soap or detergent exposure are imposed on the subjects. In order to make the test practical for use with large numbers of panelists, second basin counts are used

as a quantitative sample of the resident bacteria on the skin. Note should be made that these second basin values are influenced more by transient bacteria than the fifth basin values used in the laboratory

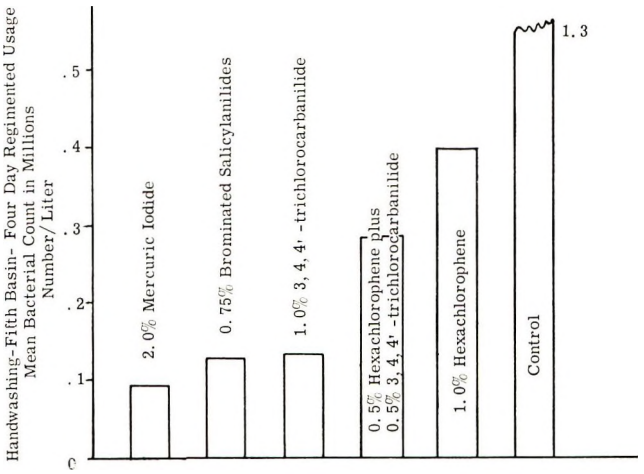

Figure 2. Skin degerming effectiveness of antibacterial bar soaps

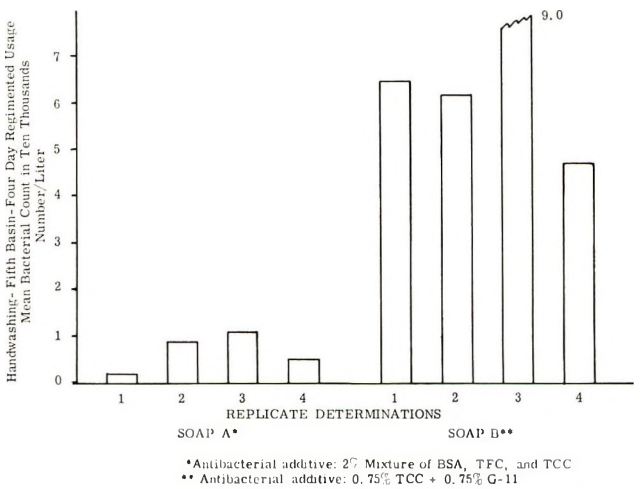

Figure 3. Skin degerming effectiveness of two different antibacterial systems

evaluations and are, therefore, somewhat less reproducible. The greater variability of the individual counts is compensated for by use of larger numbers of test subjects.

Three different consumer usage skin degerming evaluation tests will be described. The first was a test to determine effectiveness of Antibacterial Bar A relative to ordinary nonsanitizer soap. The study was run in the month of February in a northern city. Two groups of approximately 150 subjects each were sampled for the bacterial level on their hands and then were assigned on a random basis either the antibacterial soap or its control (without an antibacterial) to be used exclusively (*ad lib.*) in place of the customary bar soap product. After two weeks, the bacterial flora on the hands was redetermined. The data in Table IV show that the antibacterial soap users had a bacterial

TABLE IV

Skin Degerming: Effectiveness in a Temperate Environment under *Ad Libitum* Usage Conditions

Handwashing—Second Basin

Test Product	Mean Bacterial Count Per Liter	
	Initial Sampling	Two Week Sampling
Antibacterial soap A[a]	4,920,000	1,960,000
Control soap[b]	5,210,000	3,310,000

[a] Antibacterial additive: 2% mixture of BSA, TFC, and TCC.

[b] No antibacterial additive.

population on their hands lower than that of a comparable group using the control bar. An analysis of variance showed that this difference was significant at $P < 0.05$.

The second test was performed to determine the skin degerming efficacy of Antibacterial Bar A under hot, humid weather conditions. This study was conducted in a southern city during the month of July. Two groups of housewives were sampled for bacterial levels on the skin initially; one group was then assigned the antibacterial soap and the other the control soap without sanitizer additives. The test was conducted on a double-blind basis; neither the subjects nor the bacteriologists knew who was assigned the antibacterial product until the test was completed. The subjects were sampled for the levels of bacteria on the skin after two and four weeks of assigned product usage. The results of the handwashing tests (Table V) show again that there was a reduction in the bacterial flora on the skin of the subjects using the antibacterial soap. The difference between the bars was statistically significant ($P < 0.05$).

The results of this test, in general, corroborated the previous clinical test findings regarding the skin degerming efficacy of the antibacterial soap under *ad lib.* conditions. This test also showed that the antibacterial bar soap reduced the total skin bacterial level found on the hands as effectively in a sub-tropical climate as in a northern or temperate climate.

A third test was conducted to determine the capability of the handwashing test to detect differences in the relative skin degerming effectiveness of two antibacterial bar soaps containing different antibacterial systems. Degerming efficacy differences had already been detected under the above described laboratory handwashing conditions. The

TABLE V

Skin Degerming: Effectiveness in a Sub-tropical Environment under *Ad Libitum* Usage Conditions

Handwashing—Second Basin

Test Product	Two Weeks Usage	Four Weeks Usage
Antibacterial soap A[a]	665,000	441,000
Control soap[b]	1,381,000	1,126,000

[a] Antibacterial additive: 2% mixture of BSA, TFC, and TCC.
[b] No antibacterial additive.

TABLE VI

Skin Degerming Effectiveness of Two Different Antibacterial Systems

Handwashing—Second Basin—Ad Libitum Usage

Test Product	Mean Bacterial Count Per Liter	
	Two Weeks Usage	Four Weeks Usage
Antibacterial bar soap A[a]	649,000	657,000
Antibacterial bar soap B[b]	1,513,000	1,403,000
Control soap[c]	3,715,000	3,495,000

[a] Antibacterial additive: 2% mixture of BSA, TFC, and TCC.
[b] Antibacterial additive: 0.75% TCC + 0.75% G-11.
[c] No antibacterial additive.

test was conducted in a northern summer environment. Antibacterial Bar Soap A containing the 2% mixture of BSA, TFC, and TCC; Antibacterial Bar Soap B containing 0.75% TCC plus 0.75% G-11; and a control bar with no antibacterials were randomly distributed to approximately 500 housewives. Distribution was such as to obtain three equal-sized groups using each test bar. The test was conducted as a

double-blind study. Individual subjects were sampled for the levels of bacteria on their hands (second basin counts) after two and four weeks of assigned product usage. Over 160 subjects in each group completed the study. Results are presented in Table VI.

A statistically significant ($P < 0.05$) reduction in the bacterial flora of subjects using the antibacterial bar soaps when compared to the control group was evident at both the second and fourth week sampling. Moreover, the analysis of variance showed that the observed difference in skin degerming effectiveness between the two antibacterial bar soaps was significant at $P < 0.05$.

The ability to demonstrate statistically significant differences between two effective antibacterial soaps under normal usage conditions is evidence of the resolving power of which properly designed and executed testing techniques are capable.

Conclusions

Results of *in vitro* testing may be of value in screening for potential antibacterial ingredients. They are not reliable, however, for predicting actual skin degerming effectiveness of products. In the case of minimum inhibitory concentration tests, the results are too dependent upon the particular bacterial species or strains selected for the test to be meaningful in determining the relative effectiveness of various antibacterial bar soaps.

At the present time, the only reliable way to determine efficacy of antibacterial bar soaps is the measurement of a change in the number of cutaneous bacteria resulting from exposure of the skin of human subjects to the products. Procedures are available for conducting such studies. These are feasible not only for use under controlled conditions in the laboratory, but also for *ad lib.* consumer use studies in the field.

(Received December 2, 1965)

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Translations Available

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

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

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

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

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

J. Soc. Cosmetic Chemists, **17**, 355-360(1966)

Cyclic Salicylanilides as Antibacterial Agents

WINTHROP E. LANGE, Ph.D.,* and JON C. ANDERSON, M.S.

Presented May 4, 1965, New York City

Synopsis—A number of halogen, trifluoromethyl, and sulfur-containing salicylanilides along with cyclic derivatives of these same compounds were prepared for evaluation as antibacterial agents. The effects of structure modification on activity were shown by a densitometric minimum inhibitory concentration technique. The trifluoromethyl-substituted salicylanilides and their cyclic derivatives were found to be the most potent antibacterial agents.

Introduction

Antimicrobial agents have been used for many years in cosmetic and pharmaceutical products to protect and preserve them from deterioration due to growth of bacteria, fungi, or yeasts. Today many of the same agents are incorporated into soaps, shampoos, deodorants, toilet preparations, and the like as medicinal agents. Recently a considerable amount of interest has centered about the halogen and trifluoromethyl substituted salicylanilides (1). Investigation has also been carried on with the cyclic derivatives of various salicylanilides, namely the benzoxazinediones and benzothiazinediones which, depending upon substitution, have increased the activity of the parent molecule (2).

Thus, it has been proposed that a series of salicylanilides and cyclic derivatives of salicylanilide be prepared and subjected to antibacterial testing.

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Experimental

Syntheses

3'-Trifluoromethylsalicylanilide.—A slurry of 11.05 g. (0.08 mole) of salicylic acid and 12.89 g. (0.08 mole) of 3-trifluoromethylaniline in 200 ml. of chlorobenzene was refluxed for three hours with 4 ml. of phosphorus trichloride and was filtered hot. The solution was refrigerated overnight. The resulting precipitate was collected on a filter, washed with a 5% solution of hydrochloric acid, air-dried, and finally recrystallized from ethanol after decolorization with activated charcoal. A 45% yield of product was obtained (Table I).

2'-Chloro-5'-trifluoromethylsalicylanilide was obtained in a similar manner in 40% yield.

4'-Bromo-2-mercaptobenzanilide was prepared in a similar manner in 50% yield.

3-(4-Bromophenyl)-6-bromo-1,3-benzoxazine-2,4-dione.—4,5-Dibromosalicylanilide (1) was condensed with ethyl chloroformate or phosgene following the procedure of Stenseth (2). The product recrystallized from toluene was obtained in 36% yield.

6,8-Dibromo-3-(3-trifluoromethylphenyl)-1,3-benzoxazine-2,4-dione was obtained in a similar manner in 60% yield.

3-(3-Trifluoromethylphenyl)-1,3-benzoxazine-2,4-dione was obtained in a similar manner in 61% yield.

3-(2-Chloro-3-trifluoromethylphenyl)-1,3-benzoxazine-2,4-dione was similarly obtained in 43% yield.

3-(4-Bromophenyl)-1,3-benzothiazine-2,4-dione was obtained in a similar manner. The product was recrystallized from a tetrahydrofuran-acetone-water mixture. The yield was 47%.

Antibacterial Studies

There are many tests for the determination of antibacterial activity, but there is no single test which is infallible. Due to the differences in solubility in agar of the compounds to be tested it was thought that the reliability of the results from an agar plate method would be questionable. Thus, the bacteriostatic activity of the compounds against *Staphylococcus aureus* and *Alkaligines fecalis in vitro* was determined by a modified minimum inhibitory concentration method (MIC).

A 1:1000 stock solution of the compound to be tested was prepared by dissolving 100 mg. of the compound in a minimum quantity of either alcohol or acetone. The solution was then transferred with

aseptic technique to a previously sterilized 100 ml. volumetric flask containing Brain Heart Infusion (BHI) broth. Serial dilutions in screw-capped test tubes were made from this stock solution. To each of the dilutions of a given compound was then added 0.1 ml. of a 24-hour broth culture of the organism to be tested. The turbidity of the broth

TABLE I
Salicylanilide and Cyclic Salicylanilides

Compound	Formula	M.p. °C[a]	Calcd, %[b]		Found, %	
			C	H	C	H
3-Trifluoromethyl-salicylanilide	$C_{14}H_{10}F_3NO_2$	195–6	59.78	3.58	59.93	3.59
2′-Chloro-5′-trifluoro-methylsalicylanilide	$C_{14}H_9ClF_3NO_2$	197–8	53.23	2.87	53.44	3.06
4′-Bromo-2-mercapto-benzanilide	$C_{13}H_{10}BrNOS$	146–8	50.66	3.27	50.57	3.65
3-(4-Bromophenyl)-6-bromo-1,3-benzoxa-zine-2,4-dione	$C_{14}H_7Br_2NO_3$	141	42.35	1.78	42.15	2.35
6,8-Dibromo-3-(3-tri-fluoromethylphenyl)-1,3-benzoxazine-2,4-dione	$C_{15}H_6Br_2F_3NO_3$	233–5	38.74	1.30	38.74	1.50
3-(3-Trifluoromethyl-phenyl)-1,3-ben-zoxazine-2,4-dione	$C_{15}H_8F_3NO_3$	196	58.64	2.62	59.08	2.82
3-(2-Chloro-3-trifluoro-methylphenyl)-1,3-benzoxazine-2,4-dione	$C_{15}H_7ClF_3NO_3$	135–6	52.72	2.07	52.95	2.67
3-(4-Bromophenyl)-1,3-benzothiazine-2,4-dione	$C_{14}H_8BrNO_2S$	250–2	50.32	2.39	51.30	3.24

[a] All melting points were taken on a Fisher-Jones melting point apparatus and are uncorrected.

[b] Carbon-hydrogen analyses were conducted by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

solutions was determined with the aid of a Welch Densichron. The densitometer was chosen over visual observation for purposes of accuracy, especially when end points were questionable. The broth dilutions were then allowed to stand for 24 hours at 37 °C. A control consisting of 0.1 ml. of a 24-hour broth culture in BHI broth was also prepared and subjected to the same conditions as the compounds to be tested. At the end of the 24-hour period the tubes were again observed

with the densitometer. If growth occurred it was manifested by an increase in turbidity in the broth. The results are tabulated in Table II.

Discussion and Results

To prepare the salicylanilides, the standard procedure of reacting the substituted salicylic acid with a substituted aniline in the presence of phosphorus trichloride was employed. According to the method of LeMaire (1) the preparation of the 4′-bromothiosalicylanilide gave

TABLE II

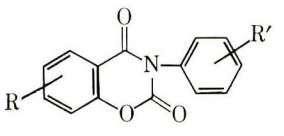
Antibacterial Activity of Salicylanilides and Cyclic Salicylanilides

Compound	Minimum Inhibitory Concentration Range × 10^3	
	Against *S. aureus*	Against *A. fecalis*
Salicylanilide	1:10–1:100	1:10–1:100
4′-Bromosalicylanilide	1:100–1:1000	1:1–1:10
3,5-Dibromo-3′-trifluoromethyl-salicylanilide	1:1000–1:10,000	1:10–1:100
4′-Bromothiosalicylanilide	1:100–1:1000	1:1–1:10
4′,5-Dibromosalicylanilide	1:1000–1:10,000	1:1–1:10
3′-Trifluoromethylsalicylanilide	1:1000–1:10,000	1:1–1:10
2′-Chloro-5′-trifluoromethyl-salicylanilide	1:1000–1:10,000	1:1–1:10
3-Phenyl-1,3-benzoxazine-2,4-dione	1:1–1:10	1:1–1:10
6,8-Dibromo-3-(3-trifluoromethyl-phenyl)-1,3-benzoxazine-2,4-dione	1:1000–1:10,000	1:1–1:10
3-(4-Bromophenyl)-1,3-benzothiazine-2,4-dione	1:10–1:100	1:1–1:10
6-Bromo-3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione	1:1000–1:10,000	1:10–1:100
3-(3-Trifluoromethylphenyl)-1,3-benzoxazine-2,4-dione	1:100–1:1000	1:1–1:10
3-(3-Trifluoromethyl-2-chlorophenyl)-1,3-benzoxazine-2,4-dione	1:1000–1:10,000	1:1–1:10

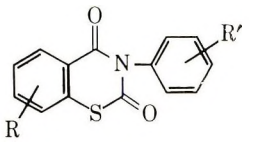
the disulfide. It was found that when the order of mixing and reflux time were altered the mercapto derivative could be obtained instead of the disulfide. Thus, when a slurry of *o*-mercaptobenzoic acid, phosphorus trichloride, and *p*-bromo-aniline in chlorobenzene was refluxed two hours, the mercapto derivative was obtained.

To prepare the benzoxazinediones (I), the procedure of Stenseth (2) employing the reaction of a salicylanilide in a mixture of pyridine and acetonitrile with ethyl chloroformate was used. All of the products were characterized by infrared spectra and carbon-hydrogen analyses. It

was found that the benzoxazinediones could be prepared by allowing an acetone solution of the salicylanilide saturated with phosgene to stand for three days. In general, the yield by the phosgene method was not particularly good.



I



II

It was thought that if an atom of sulfur were introduced into the benzoxazine molecule a more active antimicrobial agent might be formed. Thus, a benzothiazine-2,4-dione (II) was prepared employing the ethyl chloroformate procedure. The microbiological screening did not indicate increased activity of the cyclic derivative.

Attempts were made to prepare compounds containing a sulfur atom in the 2-position. It was thought that this might be done by replacing the ethyl chloroformate with thionyl chloride. Crystalline solids were obtained which were not starting material. They also contained nitrogen but no sulfur. No positive identification has been made of these products.

A comparison of the antibacterial activities of the various halogen and trifluoromethyl substituted salicylanilides with the mercaptobenzanilide showed that sulfur-containing compounds had no greater activity than compounds without sulfur.

It was also determined that the cyclization of the various salicylanilides did not produce a change in antibacterial activity. A decrease in activity was shown by the cyclization of the thiobenzanilide. It is interesting to note that cyclization, which changed a secondary amide to a tertiary amide, did not result in a change in antibacterial activity. This would suggest that the mode of action of these agents is more likely physical blockage of the pores of the cell membrane of the microorganisms rather than an actual binding or complexation within the microorganism.

Summary

A number of salicylanilides, benzoxazinediones, and a benzoxathiazinedione were prepared for evaluation as antibacterial agents. Antibacterial screening by the minimum inhibitory concentration method showed that the trifluoromethylsalicylanilides and their cyclic derivatives are potent antibacterial agents.

Acknowledgments

The authors express their appreciation to Prof. R. W. VanderWyk for his assistance in the microbiological determinations and to Stecker Chemicals, Inc., for financial assistance.

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J. Soc. Cosmetic Chemists, **17**, 361-372(1966)

BY-LAWS OF SOCIETY OF COSMETIC CHEMISTS

(Incorporated under the laws of Delaware)

As Amended March 15, 1966

ARTICLE I

NAME, OFFICES, OBJECT AND CORPORATE SEAL

SECTION 1. *Name.* The name of the corporation is Society of Cosmetic Chemists, hereinafter called the SOCIETY.

SECTION 2. *Offices.* The principal office of the SOCIETY, unless otherwise ordered by the Board of Directors, shall be at No. 100 West 10th Street in the City of Wilmington, County of New Castle, State of Delaware, and the name of the resident agent in charge thereof shall be The Corporation Trust Company, 100 West 10th Street, Wilmington, Delaware. The SOCIETY may also have offices at such other places as the Board of Directors may, from time to time, designate.

SECTION 3. *Purposes.* This SOCIETY is organized and will be operated exclusively for charitable and scientific purposes within the meaning of Section 501 (c) (3) of the Internal Revenue Code of 1954. No profit or private benefit shall inure to any persons from the income or property of the SOCIETY.

Notwithstanding any provision to the contrary, no Member, Officer or Governing Body of this SOCIETY shall be permitted to act in any manner inconsistent with the purposes of this SOCIETY and provisions of Section 501 (c) (3) of the Internal Revenue Code, or its equivalent in any subsequent Internal Revenue acts.

SECTION 4. *Corporate Seal.* The SOCIETY shall have a corporate seal which shall consist of two concentric circles, between which shall be the name of the SOCIETY, and in the center shall be inscribed the year of its incorporation and the words "Corporate Seal, Delaware."

ARTICLE II

MEMBERSHIP

SECTION 1. *Membership.* The SOCIETY shall consist of three classes of Members, namely: *Active* Members, *Honorary* Members, and *Emeritus* Members. Persons interested in the objects of the SOCIETY shall be eligible for Membership as defined in ARTICLE II, SECTIONS 2, 3, and 4, of these By-laws.

SECTION 2. *Active Membership.* The Board of Directors may elect to Active Membership persons who have (1) majored in the fields of Chemistry, Pharmacy, Chemical Engineering, Medicine, Physics, or other related sciences, and are recipients of degrees from accredited colleges or universities; or, (2) matriculated for not less than two years in an accredited college or university with recognized credit in the above stated fields of Science and who, thereafter, have been engaged in a technical capacity in the Toilet Goods Industry for not less than five years; or, (3) been deemed eligible upon examination of their qualifications by the Board of Directors. However, no more than two applicants shall be accepted in any one year under clause (3).

To be eligible for Active Membership, applicants shall qualify in accordance with one of the three stated specifications; shall file with the Secretary of the SOCIETY an application endorsed by three Members of the SOCIETY who are qualified to do so by right of full Membership privileges; and, shall pay the initial stated annual dues. If approved by the Board of Directors, they shall be elected to Active Membership by the majority vote of the Directors present at the meeting at which their names are presented.

SECTION 3. *Honorary Membership.* Any Member may nominate for Honorary Membership any person whom he deems worthy of such honor. All nominations must be made in writing to the Secretary of the SOCIETY together with reasons for conferring this honor.

The Secretary shall notify each Member of the Board of Directors and of the Advisory Committee of any such nominations received together with submitted reasons.

The Advisory Committee shall review the qualifications of each Candidate and by majority vote shall decide what recommendation to make to the Board of Directors in respect to each individual.

The Board of Directors shall then, and only then, vote on each Candidate, who shall be considered elected to Honorary Membership upon receiving at least two-thirds of the votes cast at the meeting.

An Honorary Member shall be entitled to all the privileges of an Active Member for life but shall not be entitled to vote or hold Office. He is exempt from payment of dues. However, an *Active Member* who has been elected to Honorary Membership may retain his right to vote and hold Office by continuing to pay dues.

Honorary Members are elected only by and to the National Society.

SECTION 4. *Emeritus Membership.* Any member who has reached the age of sixty years, has retired from active, remunerative work and who has been a Member for ten years, may through request or by nomination in his behalf transfer to Emeritus Membership by application to the Secretary of the SOCIETY.

The Secretary shall then refer such request or nomination to a Committee composed of the Secretary, Treasurer, and the Chairman of the Membership Committee, and upon its favorable recommendation and approval by the Board of Directors such Member shall be entitled to the designation Emeritus Member and to all the privileges of an Active Member for life, with exemption from payment of dues, but an Emeritus Member shall not be eligible for election as an Officer or Director.

SECTION 5. *Termination of Membership.* The voluntary resignation of any Active Member shall become effective immediately upon receipt by the Secretary of such request in writing from the Member.

SECTION 6. *Termination of Privileges.* All rights, powers, privileges,

obligations or duties of a Member, Director or Officer shall cease upon the death, resignation, or other termination of such Member, Director or Officer from the rolls of the SOCIETY.

SECTION 7. *Renewal of Membership.* Any active Member who shall resign while in good standing may be restored by request in writing to the Secretary of the SOCIETY and by payment of the stated annual dues for that year in which he requests reinstatement.

ARTICLE III

MEETINGS

SECTION 1. *Annual Meeting.* Each year, the Board of Directors, by a majority vote, shall set the Annual Meeting on a date in December to be held at the principal office of the SOCIETY or at such other time and place as the Board of Directors shall designate. Notice of not less than two weeks before the date of such meeting shall be mailed by the Secretary to each Member at his recorded address stating the object of such meeting.

SECTION 2. *Special Meetings.* A special meeting of the SOCIETY may be held at any time or place upon the call of the President or Secretary, provided not less than two weeks notice is sent by the Secretary to each Member at his recorded address stating the object of such meeting.

SECTION 3. *Quorum.* Not less than fifty Members of the SOCIETY shall form a quorum at any Annual or Special Meeting of the SOCIETY at which business is transacted.

SECTION 4. *Voting Privilege at Meetings.* At all meetings of the SOCIETY each Member in good standing shall be eligible to cast one vote in person. Any Member in arrears for dues shall not be eligible to vote.

All questions, presented for action, except those for which decision is regulated by statue, shall be determined by a majority vote of the eligible Members present.

ARTICLE IV

GOVERNING BODY

SECTION 1. *Board of Directors.* The governing body of the SOCIETY shall be known as the Board of Directors which shall consist of the Officers, namely: President, President-elect, Secretary, Treasurer, four Elected Directors and, to represent the established Chapters, the Chairman of each established Chapter or in his absence his designate delegate who is a Member of the respective Chapter.

All Chairmen of Chapters, or in their absence their designate delegates, shall enjoy the temporary status of Directors of the SOCIETY only while attending a meeting of the Board of Directors, but the quorum of the Board of Directors, shall not be affected in any manner by the absence of any or all representation from the established Chapters.

SECTION 2. *Authority.* The Board of Directors shall have control over the affairs of the SOCIETY, including the direction and management of its activities and the control and disposal of its property and funds. It shall have the powers and authority especially conferred upon it by the Certificate of Incorporation and by the By-laws including such right, power and authority as may be exercised by the SOCIETY in its privileges as a non-profit corporation organized under and subject to the laws of the State of Delaware, in the provisions of the Certificate of Incorporation, and in the By-laws of the SOCIETY.

SECTION 3. *Election.* The Officers and those Elected Directors elected each year, in accordance with ARTICLE VI, SECTION 3, of these By-laws, shall take office at the close of the Annual Meeting each year; and, except for the Elected Directors or when appointed to fill an unexpired term, shall serve for one year or until successors are duly elected and take office.

Elected Directors shall serve for two years or until successors are duly elected and take office. The Directors shall be so grouped that two shall be elected and two retired each year, and such retired Elected Directors shall be eligible for re-election to such office for not more than one additional term.

No member may serve as President-elect for more than three terms of office.

The Secretary and Treasurer shall be eligible to re-election to such office for not more than four consecutive terms, following which there shall be a lapse of at least one year before they may again become eligible for election to such office.

SECTION 4. *Filling Vacancies.* Whenever for any reason a vacancy shall occur on the Board of Directors, the remaining Members of the Board of Directors shall have the power to elect a Member of the SOCIETY to fill such vacancy until the next annual election.

SECTION 5. *Limitation of Privileges.* All Officers and Members of the Board of Directors shall be Members of the SOCIETY.

No Member of the Board of Directors shall receive any remuneration for service performed for the SOCIETY but upon prior authorization by the Executive Committee may be allowed reimbursement for expenses incurred for attendance at meetings or when performing duties as a Member of the Board of Directors.

ARTICLE V

BOARD OF DIRECTORS AND DEFINED COMMITTEES

SECTION 1. *Regular Stated Meeting.* The Board of Directors shall hold at least two regular meetings in each calendar year. Notice of such stated meeting shall not be necessary if such meeting is convened immediately following the Annual Meeting. Five elected Members of the Board of Directors shall constitute a quorum.

SECTION 2. *Special Meetings.* A special meeting of the Board of Directors may be called by the President at any time. A special meeting of the Board shall be called by the President or the Secretary at any time upon the request of two of its elected Members.

Notice of all special meetings to be held by the Board shall be sent to each Member of the Board of Directors, including the Chairman of established Chapters, not less than one week prior to the stated meeting.

SECTION 3. *Procedure.* The Board of Directors shall hold its regular or special meetings at the stated principal office of the SOCIETY or at such other place as it may designate. The Board of Directors may transact any business pertaining to the SOCIETY at any of its meetings.

Except wherein these By-laws require an otherwise vote by the Board of Directors, any action taken by a majority vote of the Members of the Board of Directors present at any meeting duly called and convened shall have full force and effect.

SECTION 4. *Advisory Committee.* This Committee shall consist of the President, the President-elect, and the five most recent active Past-Presidents who are Members of the SOCIETY. The most recent active Past-President shall serve as Chairman.

The Advisory Committee shall have the privilege to initiate matters pertinent to the welfare of the SOCIETY and shall consider such matters referred to it by the Board of Directors for study. It shall make appropriate recommendation to the Board of Directors.

SECTION 5. *Executive Committee.* In the Interim period of the meetings of the Board of Directors, this Committee, consisting of a majority of the Board of Directors, may meet at the

call of the President. The President shall serve as Chairman. This Committee shall have all the powers of and act in lieu of the Board of Directors, provided such action is taken by the unanimous vote of those present and that a report of its actions is submitted at the next meeting of the Board of Directors.

SECTION 6. *Finance Committee.* This Committee shall consist of the President-elect, who shall serve as Chairman; the Chairman of the Advisory Committee; and two Elected Directors appointed by the President. Three members shall constitute a quorum.

The Finance Committee shall study the Annual Budget of the SOCIETY and of each Chapter, as prepared and submitted by the respective Treasurers not later than November 1st of each year, and shall make appropriate recommendation to the Board of Directors for its considered action at its next regular meeting.

The Finance Committee shall consider and recommend appropriate action for any financial matters of the SOCIETY and of the Chapters referred to it by the Board of Directors for study.

The Treasurers of the SOCIETY and of each Chapter shall have the privilege of attendance at such meetings of the Finance Committee when the budget estimates are being considered, but they shall not have the power of vote.

ARTICLE VI

PROCEDURE FOR NOMINATIONS AND ELECTIONS

The President-elect, Secretary, Treasurer and the four Elected Directors of the SOCIETY shall be chosen and elected in accordance with the provisions of this ARTICLE of these By-laws.

SECTION 1. *Nominating Committee.* The President shall appoint three Members to serve as a Nominating Committee, two of whom shall be from the Membership at large, and such appointment shall be made not later than June 1st of each year.

SECTION 2. *Nominations.* Prior to September 15th, the Secretary shall send to each member of the Society a nomination ballot on which the Member may write in for each office the name of one Society Member and for Elected Directors the names of not more than two Society Members.

The Member shall seal his ballot in a plain envelope marked "Ballot" and shall enclose this envelope in a sealed envelope bearing his handwritten signature; and, to be valid, it must be returned to and received by the Secretary of the SOCIETY not later than October 5th of each year.

The Secretary shall then meet with the Nominating Committee to open these envelopes and count the total returns for each Member proposed and prepare an Election Ballot as directed in SECTION 3 of this ARTICLE of these By-Laws.

Any interested Member of the SOCIETY may be an observer to these proceedings, provided that such Member makes no attempt to influence the Nominating Committee or to interfere with its stated functions.

SECTION 3. *Preparation of the Election Ballot and Method of Balloting.* For each Office there may be not more than two candidates, and for Elected Directors not more than four candidates.

The list of candidates for each office shall include the name of the consenting member who has received the largest number of votes for that office on the nomination ballot, provided that the candidate so selected received the highest number of votes above five per cent of the total membership of the SOCIETY.

The Nominating Committee may place in nomination at least one candidate for each office in addition to

those determined by the nomination ballots; and it shall be the duty of the Nominating Committee to name one candidate for each office when none is determined by the nomination ballots, as herein provided.

The list of candidates for Elected Directors shall include the names of the two consenting members who shall have received the largest number of votes for Elected Directors on the nomination ballots, provided that these two candidates have received the highest number of votes above three per cent of the total membership of the SOCIETY. It shall be the duty of the Nominating Committee to make certain that there are at least two candidates on the election ballot.

If any nominee shall receive nominating votes sufficient to entitle him to be a candidate for more than one elective position, the Nominating Committee shall notify the nominee, and the Committee in consultation with the nominee shall decide that office for which he shall be a candidate.

Under the title of each position on the election ballot the Nominating Committe shall list alphabetically the names of the candidates therefor, without any other designation. The Nominating Committee shall certify to the Secretary that each person whose name appears on the election ballot has consented to hold office if elected.

The Secretary shall arrange for the printing of the election ballot as received from the Nominating Committee and shall send a copy to each member of the SOCIETY prior to October 25th. To be valid such ballot must be returned and received by the Secretary not later than November fifteenth. Election ballots so received shall be the only ballots which shall be counted.

Three tellers, none of whom is a candidate for office, shall be appointed by the President. The tellers shall receive the election ballots from the Secretary; if deemed necessary they shall verify the signatures against the master list of Members. The tellers shall count the votes and deliver to the Secretary all election ballots in a sealed package, together with a signed report certifying the number of votes for each name on the Election Ballot.

These proceedings may be observed by any interested Member of the SOCIETY, provided the Member does not interfere with the business of the tellers.

The candidates receiving the highest vote for each Office and the two candidates receiving the highest number of votes for Directors shall be declared elected. In the case of a tie vote, the Advisory Committee shall elect from the tied candidates. The results of the election shall be announced by the President at the Annual Meeting.

The Election Ballots, packaged and sealed shall remain in the custody of the Secretary until the next election unless surrendered to the tellers, by order of the Board of Directors, for the purpose of verifying the votes for the election of any officers. Any candidate shall have the right to demand a recount within fourteen days after announcement of the results has been made at the Annual Meeting.

Article VII

Officers

Section 1. The Officers of the SOCIETY shall be a President, President-elect, Secretary and Treasurer, all of whom shall be Members of the Board of Directors.

Section 2. The Board of Directors may appoint other Officers and Agents who may reside and/or act anywhere in the world. Appointed Officers need not be members of the Board of Directors. Appointed agents need not be Active or Honorary Members of the Society or of the Board of Directors. Such appointed Agents shall hold their offices for such term or terms and shall exercise such powers and

perform such duties and receive such compensation for their services as shall be determined by the Board of Directors. The appointment by the Board of any person to be an Agent of the SOCIETY shall not necessarily confer upon such appointee Active or Honorary Membership in the SOCIETY.

SECTION 3. Except for the office of President, vacancy in any office by reason of death, resignation, removal, disqualification, or otherwise may be filled by the Board of Directors for the unexpired portion of the term, in accordance with ARTICLE IV, SECTION 4, of these By-laws.

If the President should die, resign, be incapacitated, or otherwise vacate his office, the President-elect shall take over his duties until such time as that President-elect becomes President.

If both the President and President-elect should die, resign, be incapacitated, or otherwise vacate their offices on or after June 1 of any year, the most recent Past President, capable of so doing, and confirmed by the Board of Directors, shall perform all the functions of the President for the remainder of that year; a new President and President-elect shall be nominated and elected for the ensuing year, in the usual manner.

If both the President and President-elect shall vacate their Offices before June 1 of any year, the most recent Past President, capable of so doing, and confirmed by the Board, shall temporarily perform all the functions of the President; however, within one (1) month the Advisory Committee shall recommend to the Board of Directors one (1) or more Candidates to fill the Office of President. The new President shall be elected from these Candidates by a majority vote of all the surviving Members of the Board of Directors. For the ensuing year, both a President and President-elect shall be nominated and elected, in the usual manner.

ARTICLE VIII

POWERS AND DUTIES OF OFFICERS

SECTION 1. *President.* The President shall be the chief executive Officer of the SOCIETY. He shall preside at all meetings of the Board of Directors and at all meetings of the Members of the SOCIETY. He shall have general supervision, direction, and active management of the business and affairs of the SOCIETY. He shall direct the performance of all orders and resolutions as issued and adopted by the Board of Directors. He shall execute all contracts, deeds, bonds, and other instruments in writing as authorized by the Board of Directors in the name of the SOCIETY. He shall have the general powers of supervision and management usually vested in the Office of President of a nonprofit corporation under the laws of Delaware.

SECTION 2. *President-elect.* In the absence of the President, the President-elect shall exercise all the functions of the President. He shall serve as Chairman of the Finance Committee. He shall keep the Policy Manual up to date and shall distribute a copy to each Committee Chairman in January of each year.

SECTION 3. *Secretary.* The Secretary shall keep the permanent records and minutes of the meetings of the SOCIETY and of the Board of Directors, which minutes shall be signed by him. He shall keep the Membership roll of the Active Members, a separate Membership roll of the Honorary Members and shall properly record all newly-elected Members. He shall be responsible for and have access to all records of the SOCIETY, and of its Chapters upon demand by the Board of Directors, and to its Corporate Seal, which he shall affix and attest to as directed by the Board of Directors. He shall perform all such duties as are associated with the Office of a

secretary of a nonprofit corporation under the laws of Delaware.

SECTION 4. *Treasurer.* The Treasurer shall have the custody of all of the funds and property of the SOCIETY. He shall take such steps as may be necessary to collect moneys due and payable to the SOCIETY. When necessary and proper he shall endorse on behalf of the SOCIETY all checks, notes, or other obligations and evidences of money payable and received by the SOCIETY or coming into his possession, and, shall deposit the funds arising therefrom together with all other funds of the SOCIETY coming into his possession, in such banks as may be selected as the depositories of the SOCIETY, or properly care for them in such manner as the Board of Directors may direct. He shall have access to the financial records of the Chapters. He shall prepare the annual budget estimate of the SOCIETY and shall submit it to the Finance Committee not later than November 1st of each year.

Whenever required by the Board of Directors or by the President, he shall exhibit a complete and true statement of his cash account, of the securities, and other property in his possession, custody, and control. He shall enter regularly in the books-of-accounting belonging to the SOCIETY, to be kept by him for such purpose, an accurate account of all money received and paid by him on account of the SOCIETY together with all other business transactions. He shall perform all duties which are associated with the Office of Treasurer of a nonprofit corporation under the laws of Delaware. The Treasurer shall be bonded. Each year he shall cause to have published the audited Annual Report of the financial status of the SOCIETY.

SECTION 5. *Assistant Secretary* and *Assistant Treasurer.* The Secretary may appoint one or more Assistant Secretaries and the Treasurer may appoint one or more Assistant Treasurers who may, but need not, be Members of the SOCIETY and shall not on account of their appointment to such positions be constituted Members of the SOCIETY. Upon order by the Secretary any Assistant Secretary may sign any document requiring the signature of the Secretary of the SOCIETY and may affix the corporate seal thereto. The Assistant Secretaries, Assistant Treasurers, and other Agents of the SOCIETY shall be under the direct supervision of the person to whom they are appointed Assistant or Agent thereof, unless otherwise provided by the Board of Directors.

ARTICLE IX

FISCAL YEAR

SECTION 1. The Fiscal year of the SOCIETY shall commence on the first day of January in each year and shall terminate on the thirty-first day of December.

ARTICLE X

DUES

SECTION 1. The annual dues of Active Members shall be of such amount as the Board of Directors shall determine and shall be due and payable on or before January 1st of each year.

Beginning October 1st of each year the annual dues of Active Members elected during the last three months of each calendar year shall be accepted as payable for the year beginning on January 1st of the next year. A statement of dues for the ensuing year shall be sent to each Active Member during November of each year along with a notice that any Member whose dues are unpaid by April 1st of that year will cease to be a Member as of that date and lose all privileges of membership, including receipt of the JOURNAL.

Any Member in good standing who has resigned may be reinstated upon

payment of dues for the then current year; however, a Member who has been dropped for non-payment of dues shall be obligated to pay all previous arrears of dues standing in his name before he may be considered for reinstatement.

SECTION 2. Honorary Members and Emeritus Members shall be exempt from payment of dues.

ARTICLE XI

DUTIES AND CONDUCT

SECTION 1. Contravention of the By-laws and the rules of this SOCIETY, or unprofessional or unethical conduct as described in the code of ethics, shall subject the offender to censure, suspension, or expulsion, as determined by the vote of the Executive Committee, provided the accused shall have had at least two weeks' notification in writing from the Secretary of the SOCIETY stating the charges preferred.

SECTION 2. Charges against a Member shall not be presented to the SOCIETY but shall be submitted in writing to the Secretary, to be submitted to the Executive Committee within one week, who shall then, within one month thereafter, satisfy itself of the validity of such charges. If this Committee deems the accusation warrants consideration, the Secretary shall transmit to the accused a copy of the charges and cite him to appear before such Committee on a specific data to make answer in his own behalf. Should he fail to appear in person or to be represented by attorney after a second notice (sent 30 days later), the Committee shall proceed with the trial, and its action shall be final in all cases. The decision and recommendations of this Committee, together with any or all evidence upon which its conclusions have been based, shall be sealed and kept on file by the Secretary. The Executive Committee shall report (1) that the charges are not sustained; or (2) that the charges are sustained in whole or in part and that the accused be (a) censured; (b) suspended for a definite time; or (c) expelled. Censure, suspension or expulsion from the SOCIETY shall require the unanimous vote of the Executive Committee.

SECTION 3. The trial shall be conducted in private executive session of the Executive Committee.

SECTION 4. A Member suspended for a stated period of time shall automatically be reinstated at the expiration of that time.

SECTION 5. Unless authorized by the Board of Directors, Members of the SOCIETY shall not knowingly or willfully allow the name or seal of the SOCIETY or its assets to be used by any person who is not a Member of the SOCIETY. The name of the SOCIETY shall not be used in any way by any Member to further or foster the advertising of a Member or a nonmember.

SECTION 6. No debts shall be incurred on behalf of the SOCIETY by any Officer of the SOCIETY, or of a Chapter, nor by any Member unless authorized by the Board of Directors or by such authority as is delegated by the Treasurer.

ARTICLE XII

STANDING COMMITTEES

SECTION 1. At each Annual Meeting or as soon thereafter as may be convenient, the President shall appoint the Chairman of each of the following standing committees. The Chairman shall then, with the approval of the President, appoint the personnel of his state committee.

Arrangements
International Affairs
Laboratory Methods
Library
Literature Award
Medal Award
Membership

Placement
Publications
Public Relations
Scientific Program
Seminar

The President and the Secretary shall have the privilege of attending all meetings of the Committees.

Each Committee shall use the Policy Manual for guidance of its duties.

Article XIII

Internal Organization

Section 1. The SOCIETY shall be further governed by such standing rules and regulations as shall be recommended by the Board of Directors and voted upon by a majority of the Members of the SOCIETY present and voting at the next regular meeting of the Members of the SOCIETY. These rules and regulations shall be binding on all Members.

Article XIV

By-Laws and Amendments

Section 1. An official copy of these By-laws shall be kept in the custody of the Secretary who shall make the proper alterations in this copy whenever these By-laws are amended.

Suggestions for amendments to these By-laws may originate in (1) The Advisory Committee, (2) the Board of Directors, or (3) a petition presented to the Secretary and signed by not less than twenty-five Members of the SOCIETY in good standing. The Advisory Committee shall formulate all such suggested amendments and submit them to the Board of Directors together with a statement of approval or disapproval. If the Board of Directors by a majority vote approves the proposed amendment, the Secretary shall mail a copy of such proposed amendment together with an explanation and a dated ballot to each Member of the SOCIETY entitled to vote. To be valid such ballot shall be returned to the Secretary of the SOCIETY not later than thirty days from date stated on the ballot. The proposed amendment shall be adopted if approved by a majority vote of the ballots returned.

Any proposed amendment not approved by the Board of Directors within ninety days from the time it is submitted to the Secretary or the Advisory Committee may be brought to vote of the Membership in the aforementioned manner by a petition signed by not less than seventy-five members in good standing.

Article XV

Parliamentary Authority

The rules contained in Robert's "Rules of Order," current revised edition, shall govern the action of the Society of Cosmetic Chemists in all cases to which they are applicable and in which they are not inconsistent with the Certificate of Incorporation and the By-laws of the SOCIETY.

Article XVI

Chapters

Section 1. The SOCIETY shall have the right to establish local Chapters in the United States, its territories and possessions, as well as in foreign countries.

Section 2. Each Chapter shall have the following officers: Chairman, Chairman-elect, Secretary, and Treasurer. The Offices of Secretary and Treasurer, or Chairman-elect and Treasurer may be held by one person, but the Offices of Chairman-elect, Secretary and Treasurer may not be held by one person.

Section 3. All Chairmen of Chapters shall enjoy the status of Directors of the SOCIETY only while attending a meeting of the Board of Directors, but the quorum of the Board of Directors shall not be affected in any manner by the absence of any or all Chapter Chairmen.

The Chairman of a Chapter may delegate his powers described in this

Section to his designate delegate, who is a Member of the respective Chapter, to attend the meeting of the Board of Directors.

SECTION 4. In the absence of the Chairman, the Chairman-elect shall exercise all functions of the Chairman.

SECTION 5. Each Chapter shall draw up a set of By-laws under which, following approval by the Board of Directors of the SOCIETY, it shall be governed. These By-laws shall be derived from, and be adapted to, the requirements of the individual Chapters except that no provision of such By-laws shall be in contravention to any provision of the By-laws of the SOCIETY, either in fact or in spirit. Proposed amendments to the By-laws of a Chapter shall be submitted to the Board of Directors of the SOCIETY for approval before adoption by a Chapter.

SECTION 6. The Board of Directors shall have the right to amend the By-laws of any Chapter if it deems such action necessary for the protection of the SOCIETY. A unanimous vote of the elected Board of Directors is required in support of such amendment.

SECTION 7. Each Chapter shall file a set of its By-laws with the Secretary of the SOCIETY.

SECTION 8. When election of Chapter Officers occurs the Chapter Secretary shall notify the Secretary of the SOCIETY of results of such election giving the names, residence and business addresses of the elected Officers.

SECTION 9. The Treasurer of each Chapter shall prepare and submit an Annual Budget estimate to the Finance Committee of the SOCIETY not later than November first of each year.

Upon approval by the Board of Directors of the SOCIETY of the annual budget of each Chapter, a check shall be transmitted by the Treasurer of the SOCIETY to the Treasurer of the Chapter on February first of each year for $5.00 of the annual dues paid into the SOCIETY by each Member affiliated with that Chapter. This provision shall not be retroactive in any respect. This arrangement shall apply only to the Chapters in the United States, its territories and possessions, but not to Chapters in foreign countries, with whom special arrangements shall be made individually.

Prior to February first of each year, the Treasurer of each Chapter shall notify the Finance Committee of any unspent moneys remaining in the accounts of the Chapter. The Finance Committee of the SOCIETY shall have the privilege of recommending to the Board of Directors that such sums over and above $500.00 be applied to the succeeding annual budget of the Chapter or be returned to the treasury of the SOCIETY.

SECTION 10. Chapter status may be granted to not less than twelve Members who shall apply to the SOCIETY.

SECTION 11. Each member of the Society may designate his wish to become a member of any one Chapter. Such written declaration, forwarded to the Secretary of the Society, shall entitle that Chapter to receive $5.00 of each annual membership fee thereafter paid into the Society Treasury by that member while he is a member of that Chapter. A member may change his affiliation to another Chapter by notifying the Secretary of the Society of his wish to do so. At least once every three years the Secretary of the Society shall check each member's preference for Chapter membership by asking him to indicate on a suitable questionnaire either the Chapter of his choice or his desire not be a member of any Chapter. The Secretary of the Society shall notify the Society Treasurer of any transfers and shall notify the Chapter Secretaries of any transfers of members affecting their Chapters. A member may maintain membership in Chapters

in addition to the one he has designated as his primary choice by paying directly to the Treasurer of each of the other Chapters of his choice the $5.00 annual fee for Chapter membership.

SECTION 12. The Board of Directors of the Society shall have the right to revoke the charter of any Chapter which is inactive for a period of one year or is deemed to be operating to the detriment of the Society. Within two months after receipt by the Secretary of the Society of a letter signed by three Society members, stating that any one Chapter has been inactive for one year or is operating to the detriment of the Society, and setting forth supporting details, a meeting shall be held by the Advisory Committee which the officers of the Chapter concerned shall be invited to attend in order to discuss the charges. The Advisory Committee shall report to the Board of Directors at the next Board meeting, recommending the action to be taken. The Board may then revoke the charter of the Chapter by a unanimous vote of all Board members present, excepting any who are officers of the Chapter concerned.

Book Reviews

BIOLOGY OF THE SKIN AND HAIR GROWTH, edited by A. G. Lyne and B. F. Short. American Elsevier Publishing Company, Inc., New York. 1965. 806 pages, illustrated and indexed. Price $14.50.

This book is not, as the title implies, a text on the biology of the skin and hair but is rather a compendium of 46 papers which were presented at a symposium sponsored by the Australian Academy of Science at Canberra, Australia, in 1964. The collection includes: Thirteen papers dealing with assorted biological aspects of animal and human skin ranging from a short review on "Some Unresolved Problems in the Biology of Skin" by R. E. Billingham and W. K. Silvers to "Integumentary Modifications of North American Desert Rodents" by W. B. Quay; six papers on feather studies; and 27 papers relating mainly to wool and other types of animal hair. Considering the locale of the conference, it is not surprising to find that approximately two-thirds of the papers presented are concerned with topics of prime interest to scientists in the sheep growing and wool industries.

Although each of the papers (chapters) is well written by renowned experts in their respective fields, the collection as a whole is unwieldly and lacks continuity because of the wide range of unrelated topics.

Unfortunately, it has become the vogue during the past decade for sponsors of miscellaneous symposia, seminars, and conferences to publish the proceedings of such meetings immediately in book form. This is indeed a disservice both to the authors and to the scientific community since such papers rarely reach as wide a readership as would be the case if published in one of the well-known scientific journals. What is more serious is the fact that the contents of such texts are rarely abstracted and may be missed entirely by workers in allied fields. The excellent chapters on "Soluble Prekeratin" by A. G. Matoltsy, "An Approach to the Investigation of Protein Biosynthesis in Hair Follicles" by G. E. Rogers and R. M. Clarke, "Current State of Pigment Research" by G. Szabó, and "Replacement Kinetics of Integumental Epithelia" by E. J. Van Scott are

examples of such important papers which may go unnoticed by interested workers.

Many of the authors are recognized authorities in their field and are undoubtedly invited to present their work at many such conferences. It is, therefore, not surprising to find that Chapter 15, "An Electronmicroscopic Study of Genetic Errors in Keratinization in Man" by G. F. Wilgram, J. B. Caulfield, and E. B. Madgic, is practically an exact duplication of their recently published work, "A Possible Role of the Desmosome in the Process of Keratinization," which appeared in *The Epidermis* (edited by W. Montagna and W. C. Lobitz, Jr., The Academic Press, New York, 1964; pp. 275–301).

The book is remarkably free of errors and is printed on an excellent grade of white glossy stock; it is profusely illustrated with magnificent graphs, charts, and high quality photomicrographs and electronmicrographs. The papers are well documented with references, and the index is complete and of great value. While this book will make a worthwhile addition to a reference library, it is doubtful that most of the highly specialized papers, such as "Tissue Interactions in the Morphogenesis of the Feather" by M. E. Rawles, "The Structure and Development of the Squamate Epidermis" by P. F. A. Maderson, "The Hair Cycle in the Chinchilla" by A. G. Lyne, or "Hair Growth and Moulting in the Southern Elephant Seal" by J. K. Ling, would be of widespread interest to the cosmetic chemist.—CHARLES FOX—Warner-Lambert Research Institute.

CATALYTIC HYDROGENATION by Robert L. Augustine. Marcel Dekker, Inc., New York. 1965. 118 pages, indexed. Price $8.75.

The author states in the introduction that this book is intended to "serve as a digest of the literature pertaining to the synthetic applications of catalytic hydrogenation and that by its use the organic chemist, whether graduate student, technician, or experienced worker, will be able to determine easily and quickly the proper conditions to use for a given hydrogenation." As one reads the book it becomes obvious that the author fully accomplished his task and supplied the organic chemist with a factual, concise and lucid presentation of the various aspects of hydrogenation. In every chapter the author attacks the subject without lengthy introductions; mechanistic implications are omitted and details kept to a minimum by referring the reader to the original articles.

The book is divided into six chapters, each one provided with its own list of references; they include articles published in 1964.

Chapter 2 covers laboratory apparatus and techniques. It deals with various types of high-pressure, low-pressure and atmospheric-pressure equipment; the last category includes micro-hydrogenators and

techniques for hydrogenations on chromatography-paper.

Chapter 3 is devoted to catalysts and reaction conditions. After reviewing the various catalyst-systems used in hydrogenations, the author examines the effect of temperature, pressure, solvents and quantity of catalysts on reaction rate and selectivity.

Of particular interest to the organic chemist are chapters 4 and 5, which cover hydrogenations of functional groups. Chapter 4 deals with hydrogenation of olefins, acetylenes and aromatic compounds, while Chapter 5 is devoted to hydrogenation of aldehydes and ketones, carboxylic acids and derivatives, nitro groups, nitroso compounds, azides, nitriles, oximes, amines, imines and heterocycles. In a condensed form the author examines the factors involved in the hydrogenation of various functional groups, such as catalyst selectivity, stereochemistry, etc. The reactions are very well illustrated with chemical formulation.

Chapter 6 deals with hydrogenolysis of organic compounds. The pattern is the same as in chapters 4 and 5.

The book closes with four appendices describing in detail the preparation of various hydrogenation catalysts.

The organic chemist will find much use for this book. It eliminates the need for a preliminary literature survey and contains very helpful technical and chemical information.—KALMEN MOTIUK—American Cholesterol Products, Inc.

PARTICLE SIZE, by Richard D. Cadle. Reinhold Publishing Corporation, New York, New York. 1965. 319 pages, illustrated and indexed. Price $16.50.

This book deals primarily with a discussion of particles—liquid or solid—suspended in a gaseous medium. Although the book is divided into six chapters, the book actually contains only two sections, one on theory and one on practice. As is customary in books on particles—and a must in a book on particle size—much of the theoretical portion is devoted to size distribution and distribution functions. The book also considers in some detail theories of light scattering and methods for the determination of particle size, sedimentation, and related physical measurements.

Of greater interest to practicing cosmetic chemists are the chapters on application. Thus, Chapter III—Physiological Action—should be of interest to the cosmetic formulator and the plant supervisor who is responsible for the safety of employees. The last chapter of this volume deals with the importance of particle size in fine particle technology and discusses—among other subjects—industrial problems of the paint and pigment industry and of the aerosol industry, subjects of immediate interest to cosmetic chemists.

Over-all, this book is strong in theory (about 150 pages); the practical emphasis is placed on air pollution and the production of clean air

(about 100 pages). On the other hand, the portion devoted to the industrial application of particle technology appears short and almost superficial; still, this section touches on many important practical aspects. A typical example is the (too) brief paragraph on the control of particle size of therapeutic inhalation aerosols. Thus, the author states that the particles should be as small as can reasonably be obtained from a pressure package. On the other hand in the chapter on physiological action, the author correctly describes how the ratio of particles inhaled to particles exhaled depends on their size and that particles of different size are deposited in different portions of the respiratory system. It is fairly well established that—depending upon the physiological action desired—there does indeed exist an optimum particle size for therapeutic inhalation aerosols which is of the order of 1–3 micra. Admittedly, recognition of problems and raising of questions in a book of this type is proper; but this reviewer feels that the author has on occasion failed to state clearly those few answers that are available.—M. M. RIEGER—Warner-Lambert Research Institute.

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