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Review Article

Some Aspects of Toiletries Technology

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To review even part of an area as expansive as product development technology, it is wise first to attempt to establish the boundaries of the section being surveyed. If, initially, toiletry and cosmetic products together are thought of as one group, temporarily referring to this group as cosmetics, it is noted that the Federal Food, Drug, and Cosmetic Act (1) defines cosmetics in this way: "The term 'cosmetic' means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap." In this definition therapeutic claims are absent, and the items are defined essentially as being able not to correct faults or pathologic conditions but to change the effect of and/or control a natural, nonpathologic, physiological condition of the body. Another and amusing definition of cosmetics was proposed by Mercer (2). Considering the epidermis and its appendages not only as a protective coat but also as the most communicative surface we present to other members of our species, he observed that cosmetics may be considered to be those items which act upon this component of the intraspecies communication system and enhance and facilitate it. From a formulatory viewpoint, Siegal (3) raised the point that, as compared to a pharmaceutical, the cosmetic product as a whole is the final product; that is, the formulator does not normally merely create a proper vehicle for an active component. Because of this, it is possible that the average cosmetic formulator may be more concerned than the pharmaceutical formulator about the efficacy of his preparation in addition to the usual concern about stability.

Consider now a distinction within the cosmetic field: toiletries. Revson (4), in pointing out the difference between cosmetics and toiletries for a group of security analysts, noted that cosmetics are personal and intimate, whereas toiletries are far less personal, far more utilitarian, generally lower in price, and sold on a mass basis. He also observed that cosmetics usually are sold under a company name, whereas toiletries are marketed on a single brand basis.

Lest a reader think that consideration of these definitions is mere useless orientation or pointless playing with words, this author hastens to point out that exact definition is often of great importance. The Federal Food, Drug, and Cosmetic Act governs the purity, packaging, and

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labeling of cosmetics, as the Federal Trade Commission Act governs their advertising. Judicial and administrative interpretations are therefore important because of the regulatory facets of the acts, not to mention the punitive aspects. Thus, it is necessary to determine if articles are or are not cosmetics when one is determining if the provisions of the acts are applicable. Obviously, a formulation may be both a cosmetic and a drug; probably the most striking examples of this are antiperspirant products.

Definitions are also important when one considers compliance with the rules governing the excise taxes placed on toilet preparations. Morgan (5) has given an interesting account of the conundrums involved in this area. One example he has highlighted concerns the fact that medicated preparations used to protect the skin from sunburn and windburn are toilet preparations and are taxable; preparations used for the relief of sunburn and windburn are not such and are not taxable—unless they are *advertised* for the dual purpose. Other examples create distinctions which are not only hard to rationalize, but which seem not even to be based on valid criteria.

Not the least important reason for discussing these definitions is that the writer must choose an area to write about; the Revson definition will be used. This choice is somewhat arbitrary, but it is possible to give direction to this choice. If one considers which toiletry products are reasonable candidates for coverage (it obviously would be impossible to cover all), a reasonable guide may well be the amount of civilian spending on various toiletry items. Examination of a compilation of such expenditures drawn together by Olsen and his associates (6) shows that consumer spending on hair tonics, hair dressings, and cream rinses (not to mention hair sprays), that is, on hair controlling or grooming aids, and spending on external personal deodorants and antiperspirants exceeds by far spending on other toiletry products. It seems especially appropriate then to choose these two topics for review.

It will be the purpose of this article to consider the most pertinent basic facts concerning the human material (hair and sweat glands) involved in hair control and antiperspirant formulation work, to illustrate selected facets of basic research in these areas, and to discuss the testing of formulations. Thus, the basic framework which surrounds the formulator's activities will be reviewed. Of necessity, an eclectic approach has been taken. The size of the field, even limited to the areas chosen, and the resulting geometric fanout of literature references made the problem not one of deciding what to include, but what to exclude. It is emphasized that a large body of research supports and is of interest to workers in the field of toiletry products; this is as it should be. All aspects of the development of formulations—the useful fruit of the many and varied research efforts—should be understood so that such work may rest on a foundation of reason and knowledge.

Formulation work *per se* will not be examined deeply, as such information, at least as far as the standard technology is concerned, is readily available in such works as those of Sagarin (7), Harry (8), Keithler (9), and de Navarre (10). These writers have also included in their discussions, to varying degrees, material of fundamental research interest. Also notable and of special interest in this regard are the literature reviews made by Lauffer (11).

DEODORANTS AND ANTIPERSPIRANTS

Physiological Considerations

Although it is not the purpose to review here all work done on the physiology of skin, certain pertinent facets concerning the sweat glands bear discussion as they are the target of antiperspirant and deodorant formulations. Szabo (12) has pointed out that the human body has approximately three million sweat glands. These are primarily of two types. the eccrine (help to cool the body) and the apocrine (vestigial, part of the secondary sex characteristics), the latter of which are generally associated with pilosebaceous units. The ratio of these two types varies from region to region of the body, with the latter being in the minority over-all, but being more numerous in the face and the hairy areas of the body. Rebell and Kirk (13) have pointed out that these glands are subject to emotional, thermal, thermogenic (exercise), and drug stimulation. Emotional stimulation is not prominent as a sweat effector in prepubertal children, but is prominent in adults, particularly producing sweat in the axillary regions; thermogenic effects, however, can be observed in children in the axillary region. Wada (14) also noted that epinephrine (tantamount to emotional stimulation) causes sweating in adults upon intradermal injection, yet does not in children even at doses increased 100- to 1000-fold. An excellent description of the anatomy of sweat glands (with pictures) was published by Montagna (15).

With respect to the content of combined eccrine and apocrine sweat, Carruthers (16) has called attention to much data. Sweat is known to contain water, urea, creatinine, uric acid,

lipids of various kinds, many amino acids, ammonia, traces of glucose, lactic acid, pyruvic acid, sodium and potassium chlorides, vitamins, hormones, and several minerals. The solute concentration of sweat is about 0.5%; it generally has an acidic pH value.

Any discussion of perspiration would be negligent if the works of Kuno (17, 18) were not mentioned. Kuno points out that extensive attempts at classification of skin glands have been made, with none being wholly satisfactory. Broadly, the sweat glands discharge water, and the sebaceous glands discharge sebum. However, it has been found useful, as noted above, to divide and discuss the sweat glands in the two categories: eccrine and apocrine. The eccrine develop from the epidermis and have nothing to do with hair follicles; they emit substances in very low concentrations, are spread over the whole body, and act in alternating groups such that not all become activated at once, but instead, the number of glands involved and the intensity of their action increase gradually to meet the body's cooling needs.

The apocrine glands generally arise from the hair follicles, although apocrine sites exist independently of hair follicles. They develop, like the sebaceous glands, from follicular epithelium. They come into play primarily after puberty, emit many organic and fatty substances, are prevalent in hairy areas, and emit more in the manner of a total discharge, after which a relaxation or refractory period ensues.

The apocrine glands have been less studied than the eccrine, although a fair number of studies have been effected. Shelley (19) has examined the nature of apocrine perspiration and has noted that it is a fluorescent milky fluid which dried to form (like glue) a light-colored plastic solid. He also observed the existence of a latent period between bursts of activity. Apocrine sweat is evoked more so by stress such as pain, fright, or excitement than by thermal stimulation; that is, it acts as if it is adrenergically enervated. Furthermore, an apocrine response is elicited by epinephrine but not by acetylcholine; in addition, it is not inhibited by anticholinergic agents such as atropine. Additional work by Shelley and Hurley (20, 21) has shown that the apocrine glands, which function less with advancing age, are commonly associated with hair follicles but also exist at sites independent of such follicles. It seems that because of this close physical association with hair follicles, there is no complete agreement concerning the observation that apocrine glands produce regular sweat in addition to the whitish or yellowish milky material.

Differences between the two glands which pertain to the interests of cosmetic chemists were highlighted in a study by Shelley *et al.* (22). These workers showed that apocrine sweat is odorless and sterile when it is emitted, but that axillary microorganisms act on it to produce the malodor. Without such action, no malodorous materials are produced. Eccrine sweat, on the other hand, sterile or unsterile, neither has nor develops an odor. Incidentally, Shehadeh and Kligman (23) showed that the bacteria responsible for axillary odor are Gram-positive resident organisms, the coagulase negative staphylococci and diphtheroids.

Rothman (24) has reviewed the literature concerning the physiology of perspiration production and has observed the seemingly dual adrenergic and cholinergic enervation of the apocrine glands. Probably the most succinct expression to characterize the situation is that of Shelley (25): "It is the 'hot spot' rather than the 'hot room' which actuates apocrine sweating."

Products and Active Ingredients

At first it may be proper to define the difference between antiperspirant and deodorant products; some confusion exists in general and is also evident even in semitechnical trade journals. One wonders if this confusion, if not aided, at least possibly has been abetted by manufacturers whose products are ineffective antiperspirants, but who desire equality of image in the purchaser's mind for their deodorant formulations.

Antiperspirants reduce the quantity of perspiration and generally act also as deodorants, primarily because they reduce the bacterial count of the area to which they are applied so that the resident microorganisms have no chance to degrade any of the fatty or proteinaceous components of sweat to form malodorous compounds. Deodorant products, on the other hand, are in general simply perfumed antibacterial agents which function usually in the manner just stated; they also may possibly act by adsorbing the compounds having undesirable odors or, more probably, by masking the odors.

Thorne (26), in a short summary, traced the course of development of some of the many agents used as deodorants and antiperspirants. Deodorant preparations have seen the incorporation of many agents. Examples are zinc oxide and peroxide, boric and benzoic acids, and antiseptics such as hexamine, chlorothymol, and oxyquinoline. Tetramethylthiuram disulfide also has been employed as by Baer and Rosenthal (27). Although the latter compound and bithionol have been used, it is their relative, hexachlorophene,

which has today risen to prominence as a deodorant. The antibacterial quaternary ammonium compounds have been used also. Expectedly, the next step in the same field of compounds consisted of using antibiotics. Ferguson (28) employed chlortetracycline and also related that others had effectively used neomycin. It appears that cost, sensitization, and the possibility of the development of resistant strains of organisms have caused a lower acceptance of these active ingredients than they might have achieved. Partial success in both *in vitro* and *in vivo* studies was achieved by Ikai (29), who used ion exchange resins to remove odoriferous components of axillary perspiration. Winters (30) also discussed the potential utility of ion exchange resins in deodorant formulas. Cost considerations and the large quantities needed in formulations were apparently insurmountable problems. Similar partial success with much greater, albeit transient, recognition involved the use of chlorophyll, studied *in vitro* and *in vivo* (topically and orally) by Killian (31).

Antiperspirant activity has been primarily elicited by applying topically multivalent metals in ionic form. An example of such use of the metal zirconium has been described by Van Mater (32) and Helton *et al.* (33). Previous eras saw the use of aluminum, still well known, and some employment of zinc. Although other metals might be used, most activity has been limited to the three just noted because of the toxicity or undesirable side effects of otherwise potentially useful metals. It appears that the mechanism of action of these metals is not really known, although it is usually assumed that due to their astringent properties, they coagulate skin or sweat protein and thus block the sweat ducts. Incidentally, Blank *et al.* (34) attempted to determine the mechanism of antiperspirant action and designed experiments to study the degree of penetration of aluminum salts into the skin. They found that the salts are prevented from reaching the sweat glands in any appreciable amount. Their technique employed excised skin, which factor may at least partially not correspond to the actual *in vivo* situation. However, these workers concluded that the mechanism of antiperspirant action was not due to alteration of the physiology of the glands *per se*.

Studies indicate that optimum, if not all, activity is achieved by presenting the metal to the skin in ionic form. This requirement also is emphasized by work done with compounds such as aluminum and zinc phenolsulfonate. These compounds are inactive as antiperspirants, an observation which is underscored also by the fact that they do not corrode cans in aerosol preparations—one example of many of the connections commonly found between activity and side effects in both drug and toiletry work. A further extension of attempts to use essentially organically bound aluminum is illustrated by the work of Icken and Jahren (35), who suggested the use of aluminum nitrilotrialkoxides and various aluminum alkoxides. In addition to low aluminum content, the requirement that hydrolysis must take place before effectiveness is achieved imposes a serious burden on the compounds such that their utility is vitiated.

Some very interesting work on antiperspirants of another type is represented by the study of certain quaternary compounds and their amine counterparts; the fact that some of the materials are quaternaries, and thus in this respect analogous to the ionic metals, enhances interest in them. However, the fact that these compounds can elicit physiological responses seems to overbalance this structural fact. Shelley and Horvath (36) checked 15 parasympatholytic compounds for activity against localized eccrine sweating induced by the intradermal injection of pilocarpine nitrate. They attempted to determine if anticholinergic agents would prevent acetylcholine, the parasympathetic chemical mediator, from acting on the sweat gland. The compounds were administered orally, with the result that some marginal activity was evidenced in the 30–60 min. period after ingestion. When high doses were employed, the side effects were so great that these workers concluded that anhidrosis is actually a sign of overdosage. These investigators then employed topical application, hoping to localize the effects. Some of the agents had activity when used as 1% solutions in an iontophoretic procedure. Scopolamine hydrobromide was found to be definitely the best, with atropine methyl nitrate and atropine sulfate next in effectiveness. Also effective were homatropine methylbromide and scopolamine aminoxide hydrobromide. Many of the newer synthetic agents were not effective. Rechallenging of the patients showed that the scopolamine hydrobromide treated and the surrounding areas retained at least partial anhidrotic properties for periods up to 2 weeks. The effectiveness of the same agent after simple topical application from aqueous solution was maintained, and even some dose response effects were noted where different concentrations were used. Shelley and Horvath cautioned against the potential harm in using these agents if systemic absorption were to take place through abraded skin or possibly through indiscriminate

use over large areas of the body. These authors also pointed out that their study of the compounds used resulted in the same power ranking order as the materials exhibited as pilocarpine antagonists in the eye in a study by Nyman (37). It was also noted that topically applied solutions had no effect on the sweat glands of the palms and soles, as these areas, having no folliculo-sebaceous mechanism, provide no route for absorption.

Zupko (38) and Zupko and Prokop (39, 40) studied the effects of oral administration of the anticholinergic quaternary amines, methantheline and diphemanil, on hyperhidrosis and concluded that the compounds were reasonably effective but have undesirable side effects (constipation, headache, heartburn). Their studies were continued with additional anticholinergic agents.

Work along these lines has continued unabated to the present. Stoughton *et al.* (41) recently reported a study utilizing hexopyrronium bromide (AHR-483), an anticholinergic agent, as a suppressor of eccrine sweating. Another recent and extensive study, which also brings structure-function concepts into play, is that of MacMillan *et al.* (42). These workers found that a variety of anticholinergic agents, especially esters, had topical antiperspirant activity; esters of scopolamine hydrobromide were found to be most effective.

Pertinent to this discussion of autonomic agents as they have been involved in the field of antiperspirants is the work of Haimovici (43–45), who has shown that sweating in man can be elicited by adrenergic agents (*e.g.*, the epinephrine group) and inhibited by an adrenergic blocking agent (*e.g.*, dibenamine) and has concluded that in addition to the cholinergic enervation, an adrenergic component is also extant, as noted before. Possibly this component represents the apocrine gland division of the dual system effecting sweat production.

With respect to basic studies in which unusual materials were employed, Sulzberger *et al.* (46) found that the electrical polarity of substances had an affect on perspiration flow. Electropositive agents (benzalkonium chloride, cetylpyridinium chloride, and some alkali metal salts) tended to reduce sweating, whereas electronegative agents (sodium lauryl sulfate, dioctyl sodium sulfosuccinate, and potassium sulfate) tended to increase the delivery of sweat to the skin surface.

Returning briefly to the use of metallic materials, some unusual compounds were synthesized by Christian and Jenkins (47). They made aluminum methionate (*i.e.*, aluminum methane disulfonate) and reported that it had good astringent but low fabric damage potential and was nontoxic. As an extension to this work, Mantsavinos and Christian (48) synthesized as potential antiperspirants praseodymium sulfamate and the methionates of the rare earth metals neodymium, praseodymium, and samarium; Collins and Christian (49) made cerous and lanthanum sulfamate and cerous and zinc methionate. When the latter were evaluated on a molar basis, it was found that lanthanum was more effective than cerium and the latter more effective than aluminum. In other words, the ranking order followed the well-known Hofmeister or lyotropic series, which is based on the coagulative effects of ions on lyophilic sols, such as egg albumin suspended in water.

Other workers also have recommended the use of unusual metallic or organo-metallic materials. Slater *et al.* (50) suggest the use of compounds made by the reaction of aluminum chloride or aluminum chlorhydroxide with hydroxyl-containing compounds such as glycerin, ethylene glycol, propylene glycol, and similar other diols, triols, and glycols. A patent of the Schickedanz Co. (51) notes the use of the acetyl acetonate of aluminum; the compound seems to be an organo-metallic aluminum complex of acetylacetone. Grote *et al.* (52) synthesized dichloro aluminum aminoacetate as being an antiperspirant with a built-in buffer.

Noteworthy is the extensive review of many of the chemical and bacteriological aspects of deodorants and antiperspirants made by Klarmann (53).

Product Testing

Deodorants.—Testing of deodorant products is probably best done by using the nose, either directly or, in a somewhat more esthetically satisfying manner, by odor evaluation of pads worn in the axillae by subjects. However, for purposes of information, it is interesting to note a different technique which pertains to the determination of skin bacterial counts. Deodorant studies or studies of the skin substantivity of antibacterial agents may utilize techniques such as or analogous to multiple basin hand washing tests. Baer and Rosenthal (27) have described a modification of this method and have called attention to the work of Traub *et al.* (54), Cade (55, 56), and Price (57). The Baer and Rosenthal modification, which is illustrative of such attempts to monitor the efficacy of topically

applied antiseptics, generally is carried out as follows.

The subject rinses his hands in sterile distilled water, after which 5 ml. of sterile soap solution is poured into the cupped palms and worked into a lather over the hands for 1 min. up to the wrist bone. After the 1-min. lathering period, the subject rinses the lather from his hands for 15 sec. in 1 L. of sterile distilled water in a sterile 2-L. basin. The hands are allowed to drain for a few seconds and then the same process, starting with the addition of the 5 ml. of sterile soap solution, is repeated. This procedure is repeated serially five more times until seven basins have received the lather created in each case. The contents of each basin are then stirred with a sterile pipet, aliquots are removed, and a standard bacterial count study is done to determine the number of bacteria per milliliter of wash water in each basin. The test *per se* is carried out by having the subjects use a nonbactericidal soap and submit to the seven basin washing procedure at least once a week for 2 weeks; this develops the baseline count. Then the same technique is used to obtain the counts which result when the subject is using the test germicidal preparation. The number of colonies obtained in the first basin or two may be designated the transient bacterial count, and the average of the last two basins may be designated the resident bacterial count. Unfortunately, not unlike mouth or nose bacterial counting tests, the ever-present biological variation often makes interpretation of results difficult.

Story (58) also suggested a technique for testing skin disinfectants. He applied bacteria in suspension to forearm skin, after which the disinfectant under test was applied with a swab. An attempt is then made to recover surviving bacteria after various periods of time by placing a 4-cm. glass ring (also used for the applications) on the skin over the test area, adding 5 ml. of sterile distilled water, rubbing the skin with a glass rod, and then taking a 1-ml. sample for culturing purposes. Story used various bacteria which were penicillin resistant and which were isolated from wound swabs. Penicillin was added to the culture medium to suppress the growth of the normal skin flora recovered.

To eliminate the use of skin, Sagarin (59) indicated the applicability of an indirect method. This technique involves demonstrating that the compound is an effective antibacterial agent, and then deodorant efficacy is inferred. Sagarin added that the best methods of all, however, employ the human nose.

Antiperspirants, Qualitative.—To determine the effectiveness of antiperspirant formulations, essentially two types of perspiration measurements have been employed. These are visual colorimetric measurements, which are qualitative or semiquantitative (possibly useful for formulation screening), and quantitative techniques which gravimetrically measure the weight of perspiration. Such techniques generally employ pads to absorb the perspiration on insoluble materials or employ procedures which either effect air current analysis or condense the sweat prior to weighing.

Early attempts to at least partially quantitate the amount of sweat production by colorimetric means are described by Herrmann *et al.* (60). Their method was useful when applied to small circumscribed areas of the skin surface and consisted of incorporating in filter paper a powder mixture containing 5% bromphenol blue, 15% sodium carbonate, 40% cornstarch, and 40% gum tragacanth. The colored prints obtained during the test by pressing to the skin surface the treated filter paper during the sweating were then matched with standard prints produced by measured quantities of water or sweat.

Another colorimetric procedure utilizing an indicator is that of Grad (61) who, after treating the skin with an antiperspirant, applied about 6 hr. later a coat of an indicating cream containing sodium carbonate and phenolphthalein in an anhydrous oleaginous base. He then compared the number of red drops in treated and untreated areas. These and many other qualitative or semiquantitative methods have been based on the work of Wada. This investigator in the late 1940's devised a method capable of easier execution over one developed in the late 1920's by Minor. The development history of these colorimetric techniques and variations now will be reviewed briefly.

The Minor (62) method is the classic one upon which many of the indicator or staining techniques are based. Minor used 15% iodine in 10% alcoholic castor oil and applied this solution to the skin. The solution was allowed to dry, and the skin areas were then dusted with starch. Dark blue droplets are formed by the perspiration, and the progress of its formation was followed by taking pictures at intervals. Wada (14) painted skin test areas with 3% iodine in absolute alcohol, dried the area, and then repainted it with a mixture of about 40% starch in castor oil. Sweating is then observed as blue-black dots; its duration and cessation can be determined by repeatedly wiping the

spots with a dry cloth and repainting with the starch–castor oil preparation. Wada claimed that 0.05 mcg. of sweat is visible to the naked eye with this technique.

Papa and Kligman (63) improved both the Wada technique and a procedure by Randall (64), who attempted to obtain sweat patterns by pressing starch-containing paper against iodine-treated test sites. Improvement entailed painting the test site with 3% iodine–potassium iodide in 95% alcohol, drying the area, and applying a film of material consisting of about 30% starch in castor oil. After sweating is initiated and before the droplets coalesce, non-embossed absorbent paper toweling is smoothed over the surface, peeled off, dried, and covered with plastic from a spray aerosol.

Wada *et al.* (65) enhanced the known technique's ability to see sweat on dark-skinned subjects by employing titanium dioxide along with starch in a silicone oil as background. Thus, a white paste containing about 28% starch, 57% silicone, and 15% titanium dioxide is applied to a test area previously painted with a 5% iodine–alcohol solution. The appearance of perspiration is visualized as blue-black dots. These workers also modified a bromphenol blue method similarly. A 5% solution of bromphenol blue in acetone is mixed in an equal volume of the silicone oil, and after the acetone evaporates, about 10% of titanium dioxide is added to give a yellowish-orange paste. This paste, straight or diluted with petroleum ether, is then applied to the skin. Again, sweating is visualized as bluish dots. This technique is a variation of a method previously reported by Tashiro *et al.* (66), wherein a 5% solution of the indicator in acetone was mixed with an equal volume of a silicone oil, stirred until the acetone evaporates, leaving a suspension of finely divided bromphenol blue in the silicone. This suspension is applied to the skin and sweating visualized as before.

Further modifications of the starch–iodine method were reported by Papa (67). The advantages of his technique were that skin color did not interfere with it, no iodine solution is applied to the skin (such application is known to produce or prolong anhidrosis), and no interference is caused by serum exudation, and also permanent prints can be made. Papa brushed on the skin a mixture of 90% cornstarch in castor oil. Eccrine sweating produces milklike droplets. Smooth paper toweling is then applied, peeled off, and then exposed to sublimating iodine, which causes the appearance of blue-black dots on the paper. Permanence of the prints is achieved by coating the dried sheet with a plastic aerosol spray.

Another variation of the indicator method is illustrated by the work of Brun (68). His Prussian blue test employed 35% ferric sulfate anhydrous and 65% potassium ferrocyanide anhydrous; the finely ground materials were put on tape which was pressed to the sweating skin, with, upon its removal, sweating being visualized as blue dots. Sulzberger *et al.* (46) employed an indicator technique which used a preparation containing 10.5% quinizarin, 9% sodium carbonate, and 80.5% PEG 1500.

Antiperspirants, Quantitative.—Probably the most popular method used to measure perspiration quantitatively is illustrated by the work of Stoughton *et al.* (41). Essentially, the method entails obtaining baseline weights by a gravimetric procedure in which perspiration is collected on axillary pads while the subjects are in a hot room having temperatures of about 100 to 105°F. and a relative humidity of 60–90%. Baseline weights are obtained for both arms separately since they differ from each other with respect to handedness; for example, right handers sweat more on their right sides. Perspiration is collected similarly, as in the baseline determinations after treatment with the formulation under test. It is usually found that after a maximum treatment period of 1 to 2 weeks, no further significance can be added to the results; that is, there is a build-up of effectiveness only for the first days of treatment after the pretreatment period. During the treatment period, only one arm is treated. For example, if the right arm were used, the per cent inhibition is found as follows. This treatment of the data attempts to neutralize special or unique happenings caused by the test itself or by the nature of the day of testing.

$$\% \text{ Inhibition for right arm} = 100 - \left(\frac{\% \text{ of base for right arm on test day}}{\% \text{ of base for left arm on test day}} \times 100 \right)$$

where

$$\% \text{ of base} = \left(\frac{\text{wt. of sweat on test day}}{\text{wt. of sweat during baseline study}} \right) \times 100$$

Obviously, to enhance the validity of the experimental set-up, cross-over procedures are used so that each arm receives both the formulation under test and acts as a control.

Some early work on the quantitative measurement of axillary perspiration was done by

Fredell and Read (69). They used a gravimetric technique which required the weighing of pads but did not employ a hot room. Instead, the subjects perspired only due to their normal activities.

Another well-known quantitative technique is illustrated by the work of Jenkins *et al.* (70). In their technique the axillae are covered with cups having two ports; dry metered air is pumped into one port and exits from the other. A tube from the exit port is led into a metal U-tube in a cold trap; the perspiration is condensed, and the metal tube is weighed to determine the amount.

Richardson and Meigs (71) suggest a method similar to that of Jenkins, except that the perspiration is collected in a U-tube on a dehydrating agent.

Quantitative techniques such as those described above are capable of showing perspiration inhibition per cents with a good degree of reproducibility in the range of about 10 to 80%.

Daley (72) implemented experiments designed to study the suitability of using the skin of the back, as distinct from axillary areas, in quantitative antiperspirant studies. Such procedures are more convenient, as they are subject to fewer experimental difficulties. Instead of measuring perspiration volume gravimetrically as by weighing pads, this technique essentially measured area with the aid of an indicator cream; the number of drops in a treated area were compared to the number of drops in an adjacent untreated area. Daley's conclusion was that the back method is more rapid and convenient and gives in general comparable results to axillary methods. One exception found was that cream products, which form a surface coating, show much greater reduction of perspiration in the back test.

Wooding *et al.* (73) suggest a method of measuring perspiration which employs small perforated containers of dehydrated silica gel taped to the subject's skin for 3-hr. periods. No attempts to induce abnormal sweating rates were made; these investigators felt that experimental arrangements which do may tend to obscure the ranking order of the series of antiperspirants tested.

Although it is not strictly pertinent to our present discussion, it is interesting to note that Killian and Panzarella (74) collected perspiration for purposes of analysis by placing nude subjects in rubber bags which covered the entire body except the head and neck. The subjects were then placed in tubs of water gradually heated to about 45°.

A different type of *in vivo* technique was used by Collins and Christian (49). They tested antiperspirant efficacy by a gravimetric procedure which involved collecting sweat from the thoracic region of a horse. The animal was placed in a hot room and covered with blankets to stimulate sweating.

To conclude this discussion of *in vivo* quantitative methods of testing antiperspirants primarily on human beings, some final remarks may be appropriate. It is obvious that the establishment of suitable controls and baselines are vital to the foundation of valid antiperspirant panel studies. It is known that axillary sweating is influenced by many factors in addition to the emotional and thermal conditions of the subjects. These factors and others were discussed by Reller (75), who demonstrated their importance in the consideration of experimental design. Fredell and Longfellow (76) also presented suggested operational details for carrying out antiperspirant tests. Jacobi and Heinrich (77) also drew attention to factors which should be considered when a test is being planned in their fine overview of the various techniques of perspiration measurement.

Not to be neglected for purposes of discussion are attempts to check the effectiveness of antiperspirant preparations by *in vitro* techniques. Govett and de Navarre (78) have mentioned the use of one of these techniques. Although it is recognized that they are generally not completely satisfactory, the procedure utilizes a protein precipitation test in which to egg albumin and water in equal parts (5 ml.) is added 1 ml. of test solution. The presence of precipitation, the speed of formation of any precipitate, and the existence of insolubility after a period of 12 hr. are checked. Urakami and Christian (79), in one attempt to further refine the *in vitro* evaluation of antiperspirant formulations and active agents *per se*, developed a technique utilizing the permeability of frog membrane. The method was based on the previous observation that the permeability of the membrane to iodide and sodium ions increased after treatment with aluminum salt astringents. A few years later, two studies by O'Malley and Christian (80) considered additional means for monitoring perspiration flow. They attempted to refine the technique of air current analysis by using an electroconductivity method employing an electrolytic cell containing a methanol–acetone–oxalic acid mixture, which is sensitive to small amounts of water. The perspiration is collected by passing dry nitrogen gas

through a cell which encloses a small area of skin. The mixture picked up by the gas is then delivered to the electrolytic solution for assay.

Fabric Damage.—One additional aspect of antiperspirant product testing concerns damage to the fabric of the user's clothes. The full causes of fabric damage are not known, but it appears that the hydrochloric acid from some active agents can degrade fabric and also flex abrasion can result from deposit of solids, such as aluminum oxides and hydroxides, which form on or in the fibers of the cloth. These deposits can also lower the tearing strength because of their stiffening action.

The damaging potential of antiperspirant formulations can be assessed in a number of ways. Probably the most common involves the determination of the reduction of tensile strength of the fabric.

One of the most well-known techniques for assessing fabric damage is that described by Bien (81). It is known that fabric damage may result from contact with products of low pH. Bien found silk, wool, and acetate rayon are relatively resistant to low pH's, whereas linen, cotton (most commonly used in test procedures), and viscose rayon are vulnerable. Maximum damage is caused by ironing without laundering, although the presence of a buffering agent will reduce it. In this context a buffering agent is a compound which will release alkali under conditions of raised temperature; glycine and urea are probably the most commonly used agents.

The Bien test consists of applying a uniform amount of product (about 2.5 Gm.) to a 1-in. wide strip down the center of a piece of cotton 6 by 21 in.; the cloth is then incubated for 24 hr. at a relative humidity of 85% at a temperature of 80°F. The cloth is then ironed (product side down) for 10 sec. at about 285°F. Next the cloth is reincubated for 3 hr. after which the tensile strength of the treated material is compared to that of controls to which no product was applied but which had otherwise been similarly treated. In attempts to correlate this test against home usage, it was shown that reductions in tensile strength of less than 20% were, in essence, not damaging. Bien (82) later presented a further review of fabric destruction caused by antiperspirant formulations, perspiration, and various ironing and hot air treatments.

In addition to the standard breaking, tearing, and flexing tests done on cotton cloth after various laundering procedures and/or treatment with perspiration, a fabric damage measurement of some extra interest involves a fluidity technique. The essence of the method is that the cotton's cellulose, some of which is degraded due to treatment and some of which is not (or is minimally so) because it came from the control, is dissolved in cuprammonium hydroxide or cupriethylene diamine hydroxide solution. The fluidity of the solutions is then taken with a viscosimeter of the pipet or Ostwald type wherein the efflux time of the exiting fluid is measured. In this ASTM technique (83) the lower the fluidity (*i.e.*, the higher the viscosity), the lesser is the amount of damage.

HAIR CONTROL

Introduction

This section, despite its title, will not cover hair grooming products specifically, even in the sense that active agents were discussed at some length under *Deodorants and Antiperspirants*. Rather, both the macro- and microcharacteristics of hair will be described along with some of the types of hair and product research most common in the field.

In general, active agents are sought which enable one to consider such grooming concepts as set, manageability, luster, gloss, highlights, sheen, softness, body, greasiness, tackiness, and general hair feel. To translate such concepts into products, one must consider the active agent's ability to adsorb on the hair and be substantive to it, to penetrate, to soften, and to neutralize static electricity and form films on hair. To do these many things best with the myriad agents available requires knowledge of hair itself. This section will then, as stated, review hair research and describe some methods used to determine if, and to what degree, a product has achieved its grooming and controlling goals.

General Considerations

To put the subject of hair research in a proper setting, it will be convenient to discuss first the general nature of hair itself, following, in part, the treatment of Harry (8). By way of general comment, we may indicate that the life span of a hair varies in individuals from about 180 to 200 days. The number of hairs on a normal human head varies from about 100,000 to 140,000; blonds, who have the finer hair, tend toward the upper limit, whereas dark-haired persons tend toward the lower part of this range. Needless to say, with advancing age one usually finds oneself, to coin a homonym, "falling heir" to a lesser number of shafts. Hair shaft diameter

varies from about 0.05 to 0.1 mm., *i.e.*, about 0.003 in.

Ebling (84) has described the cyclic activity of hair follicles. This subject will not be expanded upon at all, except to indicate that the follicle produces hair at a rate of about 0.35 mm. per day (range 0.1 to 0.4 mm.) and that the little ball seen at the end of a plucked hair is not the root or the follicle, and its extraction will not result in permanent loss of hair from the particular site. Much more information presented at a conference on the biology of hair growth has been drawn together by Montagna and Ellis (85).

Hair and wool, which incidentally resembles hair in basic composition so that some aspects of textile technology are transferable, are made up mostly of the insoluble protein keratin. It should be appreciated that the amide links do not guarantee the stability and insolubility so evident in keratin as exemplified by hair and wool. Hair protein has other structural characteristics, not common to all proteins, which make it different. These additional features are due to other bonds besides the basic amide links which are the cohesive backbone of polypeptides; such bonds can form either between the amide groups or the R groups of the constituent amino acids.

Bonds which form between the amide link's two functional groups, the imine and the carbonyl, have a sort of incomplete acid-base character and consist of a partial hydrogen atom transfer; such H-bond interactions are possible wherever the polypeptide chains can approach one another.

The other main possibilities of bond formation between polypeptides are due to the R groups whose penchant for interaction is exercised in three ways. The first is through true salt formation between the acidic and basic residues of certain R groups, *e.g.*, the acidic groups of aspartic acid, proline, and glutamic acid and basic groups of proline, arginine, lysine, histidine, and tryptophan. These same acid and basic groups can also form amide links intermolecularly just as they formed intramolecularly; this is the second of the R group bonds. The third way that R groups interact to impart strength and insolubility to keratin is through the cystine residues, which comprise about 15% of the polypeptide chain on a weight basis or 9% on a molar basis. Cystine, having two carboxylic and amino groups, can enter into and link together (through bridge formation) two polypeptide chains through a disulfide bond.

X-ray diffraction studies indicate that, in addition to the above-mentioned features, hair possesses to a great extent a *regular*, crystal-like structure. The most widely accepted of the possibilities for describing this regularity is that of Pauling and his colleagues (primarily Corey) and consists of a helix. The helical structure may be considered to be a spiral of the polypeptide chain which incorporates about 3.6 amino acids per turn of the helix so that H-bonds are formed by the imine and carbonyl groups of amino acids separated by two other residues; the latter project outward from the general axis of the helix. The helix diameter is about 10 Å., and the distance between layers is about 5.44 Å. The molecular helices are combined into larger helices somewhat akin to the familiar intertwined structure of a rope. This compound helix is a seven-strand cable, 30 Å. in diameter. These cables are then also grouped and run side by side along the long dimension of the molecules. The interstices are filled with other helices. The many cables, large and small, are covered with sheaths—one more factor which contributes to the stability of hair.

Hair Research

Carruthers (86) stated that: "Little research has been done on human hair although millions are spent annually upon its grooming." This author is not convinced that the term "little" is appropriate, but the statement was made in the context of a compilation on the biochemistry of the skin and is probably, therefore, quite valid. Nevertheless, Carruthers noted that work has been done on such varied aspects as the determination of the metal content of hair, on the biosynthesis of hair keratin, on a study of the presence of pantothenic acid and an arginase enzyme (hair has a large component of arginine in its composition), and other enzymes. When the amino acid content of hair is compared to that of wool, many similarities are noted, particularly with regard to the arginine, glutamic acid, glycine, and serine fractions. This is fortunate as some insight into hair can be gained by the cosmetic chemist, as alluded to before, from work done on wool by textile chemists.

Parenthetically, it is interesting to note that analyses of the relative frequency of the amino acids in keratin indicate that acidic side chains occur about twice as frequently as basic side chains. This excess of acid groups, when considered within the framework of protein isoelectric point concepts, illustrates why the isoelectric point of keratin is about 4 to 4.5; Rothman (87) variously lists the isoelectric point of keratin and the horny layer of the skin surface as being

in the range of 4 to 5. Thus, it is apparent that removal from this pH will result in some swelling (as a charge will now be present), and also it has been found that quaternaries (as in creme rinses) are substantive to hair since at pH's above 4 or 5 the protein is negatively charged. In this regard, Botwright (88) found that stearyl dimethyl benzyl ammonium chloride improved the texture of hair and made it soft and manageable, and Hilfer (89) has pointed out the usefulness of many quaternaries which, when applied to the hair, greatly improve its combing properties. Another type of compound shown to be substantive to hair is illustrated by the work of Nelson and Stewart (90), who studied the adsorption of *N*-acylsarcosines on various proteins including hair. They used ^{14}C-tagged compounds and showed that adsorption was relatively even along the hair shafts, that is, the materials were not entering through the cut ends.

With respect to further definition of hair morphology, obviously, microscopic techniques are used. Grossly, hair consists of three roughly concentric sections. Outermost is the cuticle or fish-scale-like covering; next is the cortex, the main section of the hair consisting of cigar-shaped bundles honeycombed in a structure of protein material running through the cortex; and innermost is a small section, the medulla.

Randebrock (91, 92) has gathered together in two excellent and extensive articles much information on the known morphology of hair and also has related the results of his own investigations in which he used the electron microscope to study the fine structure of hair. Not to be outdone by the organic chemists, he has suggested the term "metacortex" to describe some of the features of human hair. By way of further explanation of these cortical matters, Dusenbury and Jeffries (93) in an interesting article discussed the effect of the bilateral structure on the chemistry of keratin (wool) fibers. This bilateral structure runs the entire length of the fiber and corresponds to the fiber's crimp, in fact, it is helically in phase with it as shown by staining techniques. One section is called the paracortex and the other the orthocortex. Thus, Randebrock's metacortex has completed the familiar triad.

Other workers also have contributed to the development of microscopic techniques. One should record the work of Berdick and McDonough (94), who presented a good discussion of the special problems of technique involved in use of photomicrographic methods of studying hair. Courchene (95) also reviewed electron microscope procedures for the study of hair fibers, and Keil (96) studied hair damage and swelling caused by permanent waving solutions and showed the applicability of the polarizing microscope in visualizing these factors. His published findings were illustrated with many color pictures.

Probably the most studied of physical changes in hair are swelling and stretching phenomena. Eckstrom (97) studied hair swelling by microscopically measuring the increase in diameter of single human hairs following their immersion in certain test thioglycollate solutions. He described an apparatus permitting observation of a single hair while swelling and showed its applicability. Valko and Barnett (98) also pointed out that the cosmetic processing of human hair generally involves swelling. Theoretical import lies in the relationship of the chemical structure of hair, that is, the organization of the polymers. Besides X-ray studies, observations of swelling behavior have probably done more than any other technique to shed light on the submicroscopic behavior and structure of hair fibers. Valko and Barnett studied swelling, or the lack thereof, of hair in various aqueous solutions gravimetrically. Their technique involved centrifugation of the treated hairs to remove the excess liquid clinging to the surfaces and capillary pockets formed by the matting of individual fibers. The increase in weight after immersion was then determined. The aqueous solutions employed were those of ammonium thioglycollate, alkali metal halides, ammonium halides, hydrochloric acid, sodium hydroxide, acetonitrile, diethylene glycol monomethyl ether, formamide, ethylamine, acetic acid, and triethanolamine. In a subsequent study, Powers and Barnett (99) used the same technique to study the swelling of hair in various thioglycollate solutions and demonstrated the marked effect of both pH and concentration.

Continuing studies aimed at the elucidation of the basic mechanisms involved in dyeing and wet processing of fibers were carried out by Barnard *et al.* (100). They studied human hair in sodium and lithium bromide solutions and again showed that swelling is due to the uptake of water and of salt on sites within the fiber. This swelling is greater than that produced by water alone.

Hamburger *et al.* (101) wanted to get at the fine points of the behavior of stretched hair. They studied immediate, delayed, and permanent elastic deformation to enable them to obtain better interpretations of stress-strain graphs. They also checked the stress needed

to extract a hair and to rupture it; the former was about half of the latter. These workers showed the feasibility of depicting the extent of hair damage from its elastic behavior. From a consideration of chemical concepts, the impairment of the structural state must be followed by impairment of mechanical behavior. These investigators used a sonic method which utilized the relationship of the modulus of elasticity (force per unit cross-sectional area per unit of strain; *i.e.*, the ratio of total stress to elastic strain) to the velocity of pulse propagation. Thus, a pulse propagation meter was used, essentially to measure length, by determining the time for an individual pulse to propagate a given distance as the specimen was loaded in a tensile testing device. More applications of the technique were also suggested.

Hirsch (102) continued the study of attempts to correlate the physical behavior to the chemical structure of hair keratin. He made use of the observation that human hair rotates around its own axis when it is stretched. This investigator concluded that his findings corroborated on a macro scale the known helical structure of proteins as the hairs were becoming uncoiled upon being stretched.

Whewell (103, 104) has presented recent reviews of some aspects of the chemistry of hair with special emphasis on changes brought about by various setting processes.

To expand upon some of the studies on wool and analogous fiber work alluded to above, we may note that only a small amount of the literature is being cited here. Obviously, consultation of the textile literature will reveal more of the types of methodology used and the results obtained.

Harris *et al.* (105) studied the elasticity of wool and related it to chemical structure. Interestingly, these workers organized some of their thoughts around the idea that wool is in many ways analogous to rubber and may serve as a useful model for explaining certain properties of the latter. As noted, the cosmetic chemist uses a similar analogy, except that wool is compared to hair. We recognize that wool, rubber, and hair have molecular configurations that allow its fibers to be straightened out during the stretching process; also—and this technique in addition to swelling studies is much used to study hair—wool and hair give similar curves when one plots per cent elongation *versus* load in a stretching study. Both wool and hair have cross-links which can be ruptured and rebuilt at will. Barnard and White (106) studied the swelling of hair and a viscose rayon monofil in aqueous solutions of alkali halides and hydrochloric acid. The solutes, especially lithium chloride and bromide, but not sodium chloride, caused swelling beyond that (greater than 25% for hair) caused by water. These investigators concluded that the solutes were absorbed by the fibers as a high degree of swelling was caused by successive replacement of the immersion medium by increasingly concentrated solutions. Immersion of a water-swollen hair in a concentrated solution resulted in deswelling. If the fiber is impermeable to solute, a decrease in swelling would result because of the lowering of the vapor pressure of water by the solute. If the solute is absorbed appreciably, this decrease in swelling can be overbalanced by an increase resulting from the absorbed solute with an over-all increase in swelling as the net result. Thus, osmotic absorption of water is caused by the absorption of ions. If, however, water within the fibers fills a system of micropores and the solute is not specifically absorbed by the fiber, the solution will fill the micropores without producing any change in the volume of the fiber. Barnard and White also studied the acid dyeing of keratin fibers and found that four factors influence swelling: pH, the dye, added salt, and temperature. Using a microscopic technique, they measured two profiles of single strands at 15 points and then calculated the cross-sectional area as an ellipse. They also recognized that the cystine content of hair, being greater than that of wool, results in an increase in the concentration of sulfur cross-links to make hair more resistant to swelling. The pH effect on the swelling of keratin fibers (wool) and hair was studied in the range 0 to 4.5. Maximum swelling was found with hydrochloric acid at a pH of 1.

Speakman (107) reviewed in detail much of his own very interesting work and that of others concerning mechanochemical methods for studying animal fibers. He discussed the obtaining and interpretation of load-extension curves, the use of supercontraction studies (certain reagents which are capable of causing disulfide bond breakdown cause fibers to contract to a length less than their original), and permanent set (certain treatments hydrolyze the disulfide bonds and thus dissipate stress in a stretched fiber, and then cause new cross-linkage formation to fix the relaxed structure permanently in its deformed state). These methods were shown to be useful both for routine control of textile processing and for furthering basic knowledge of the chemistry of animal fibers.

Somewhat related to the swelling studies are experiments involving the uptake of various salts by hair fibers. Along this line Stam and White (108) applied radiochemical techniques to study the interaction of hair fibers with aqueous ionic solutions (sodium bromide, sodium bromide–hydrogen bromide, and sodium chloride, with ^{22}Na and ^{82}Br) and an acid dye bath containing a sulfur-labeled (^{35}S) acid dye for wool. They pointed out that, at least qualitatively, hair and wool exhibit the same behavior. Their technique involved immersing hair in solutions of the tagged salt, removing and washing the fiber, and then measuring the radioactivity. They observed uptake of all compounds and noted that sodium chloride was less absorbed than sodium bromide.

White and Underwood (109) using ^{22}Na and ^{82}Br studied the absorption and diffusion of alkali bromides and sodium sulfate by hair. They attempted, where possible, to apply and use Fick's law. They showed that both the rate and equilibrium properties of ions absorbed by hair are strongly influenced by the structure of the hair, that is, the nature of the polymer network and the ionic groups attached thereto.

Berth and Reese (110) used a study of copper adsorption on hair keratin to monitor hair damage; they pointed out that the textile industry also uses study of copper uptake similarly. The adsorption of copper tetrammine mirrors oxidative, reductive, and ultraviolet-caused damage. Such damage manifests itself by changes in keratin structure, such that more treatments or insults result in more copper being taken up. Edman and Marti (111) observed damage to bleached hair by this technique also.

Another facet of absorption-adsorption—really diffusion—studies concerns the estimation of pore sizes, a factor of potential interest to formulation chemists. Harrison and Speakman (112) in a different type of study did very interesting work on the pore size of wool keratin. They pointed out that previous work showed that when wool was stretched in a series of primary alcohols, the resistance to extension in *n*-butanol and *n*-pentanol was equivalent to that in dry air. They concluded that the fine structure of wool is inaccessible to molecules larger than *n*-propanol. The present study consisted of observation of the known reaction that the tyrosine side chains of wool can be iodinated to form 3,5-diiodotyrosine when exposed to iodine in ethanol solution. In this work the reaction was run in other alcohols, namely—methyl, ethyl, *n*-propyl, *n*-butyl, and *n*-pentyl. They found that the iodination proceeds to completion when the reaction is run in methyl and ethyl, but that it proceeds less than half way (probably on the surface only) when run in propyl, and proceeds essentially not at all in the butyl and pentyl. Again, they conclude that the fine structure of wool is inaccessible to molecules larger than propanol. Although no direct application to cosmetic technology is obvious and although the preswelling of hair could alter the picture somewhat, as will be noted, there are obvious implications (if hair is like wool in this regard) which would lead one to choose certain agents and exclude others if penetration of hair is desired.

Edman and Marti (111), as part of a study of the properties of peroxide-bleached hair, noted that although hair differs from wool in this respect, on the basis of the results of stretching tests, alcohols having a molecular weight greater than that of methyl alcohol are not capable of penetrating the hair. Wilmsmann (113, 114) also observed the importance of penetration to dyeing and discussed the pertinence of molecular weight concepts to hair and textile coloring and comparative studies of the two. In a study involving microscopic investigation of hair dyed with dyes of various molecular diameters, he concluded that a diameter of 6 Å. is the critical size above which penetration into the hair cortex is prevented.

Holmes (115) studied diffusion processes in human hair. He observed that the appearance or shape of hair is altered by introducing foreign molecules onto and into the hair. As noted, prior work showed a 6-Å. limit; if hair is swollen, the limit should be about 35 Å. This investigator measured the diffusion constants of certain dye compounds in hair and in water and thereby attempted to determine the pore size of the hair. The essential principle used was the observation that the diffusion constants of molecules are affected when the molecules are passing through a barrier containing holes in such a way that the size of the holes can be estimated; *i.e.*, the diffusion constant, molecular radius of the material diffusing, and viscosity of the medium are interrelated.

Product Testing

Factors which affect the design and analysis of product performance in human tests (*e.g.*, half-head techniques) were discussed by Cryer (116); the obtaining of statistically valid results is not easy. Always to be preferred are instrumental measurements—even of an *in vitro* type, if possible—and in some cases this type of study can be done (*e.g.*, foam volume and viscosity of a shampoo). Often, however, humans are needed.

Both tests on humans and instrumental techniques are possible.

Boyle (117) described some applications of half-head techniques and gave suggestions pertaining to the operation by a trained beautician of a cosmetic clinic. Such a facility is better controlled and the results subject to more objective evaluation than with home-conducted tests. Such a clinic can function usefully both with respect to bolstering the quantitative aspects of advertising claim support with the usual concomitant legal niceties, and in a practical manner the clinic can help evaluate and observe a product's consumer benefits.

It is not easy to measure hair luster. However, Rosekrans (118) described a procedure utilizing a recording goniophotometer using the principles discussed by Hunter (119). Hunter reviewed the subject of gloss evaluation of materials and pointed out that it is a property somewhat difficult to measure; what is measured is the reflectance capacity of surfaces. Unfortunately, no single reflectance scale exists which is suitable for all types of surfaces; hence, a separate scale results upon study of each type of surface. The descriptive reflectance terms "specular" and "diffuse" refer, respectively, to the part of light reflected somewhat like a mirror (responsible for glossiness) and the part of light reflected diffusely. It is specular reflectance that gloss meters (light source, photocell, readout microammeter) record; an adjustable angle gloss meter is called a goniophotometer. In hair work, gloss is usually referred to as sheen, which is shininess at grazing angles. The Rosekrans procedure entailed taking a 5-Gm. switch of hair, shampooing and drying it, then measuring the luster without the application of any hair dressing. Upon completion of this measurement, 200 mg. of hair dressing was applied with a dropper. The switch was then combed in one direction for 30 sec., alternating sides of the switch. The luster of the treated switch was then measured. The goniophotometer results were expressed in luster value units, with readings ranging from 77.5 to 88 when various test agents were applied. Some sample results were: 76 (ethanol treated), 77.5 (clean switch), and 87 (mineral oil treated).

Thompson and Mills (120) also described an instrumental technique for measuring the luster of hair. Prime difficulties were caused by the great sensitivity to sample geometry (especially the angles of incidence of the light used) since this makes the adaptation of gloss meters, as used for example in the paint industry, to measurement of hair luster difficult. It is difficult to get hair to conform to a plane. To be useful, an instrument must distinguish between specular and diffuse reflectance. For best results, a high ratio of gloss or luster to diffuse reflectance is desired. The present authors were able to, in essence, make hair a plane by winding it around a 4-in. cylinder and then aligning it (the long way, not crosswise, with respect to the hair) with the optical system and path of propagation of the light. Measurements were made with a photometer. It was found that similar cylinders could be used to measure hair luster on humans after half-head treatments. Luster meter readings differing by about 4% were detectable by the eye. Thompson and Mills illustrated the applicability of the instrument and gave a sample case in which a 17% difference in favor of the syndet was found when a soap was compared to a synthetic detergent in a shampoo study.

Besides the luster of hair, other properties of groomed hair are important.

It is apparent that in hair work the estimation of properties such as manageability is often a subjective matter. Yet mechanistically speaking, these properties must be composites of more fundamental properties, and it is these which might be measured. An attempt at such measurement is illustrated by the work of Mills *et al.* (121). They observed that flyaway and combability of hair are related to the presence of and the rate of dissipation of static charges. They also pointed out that the textile industry has done work in this area of static charge measurement. These investigators developed a method which showed objectively the differences between untreated hair and hair treated with cationic species. Their method consisted of allowing a tress to acclimate itself in a closed cabinet of controlled humidity. The tress was combed in a standardized way and the ballooning of the hair noted. This fundamental technique was then quantitized by measuring electronically the charge imparted to the comb. The charge was visualized with an oscilloscope and camera. Further refinements were made in which humans were used along with an electronically outfitted comb.

Barber and Posner (122) presented a simpler method for studying static electricity produced on hair by combing. In their method the comb was put in proximity to a freely suspended strip of gold leaf, and the distance at which the leaf started to be attracted to the comb was measured; the magnitude of the charge is proportional to this distance. The whole operation of combing the switch was done in a chamber of controlled humidity. The effectiveness of

quaternaries in reducing the charge was again demonstrated.

Schwartz and Knowles (123) noted that combability, manageability, softness, and overall hand-feel are determined by the static and kinetic frictional coefficients of hair. They reviewed methods used in the textile industry and chose a dynamic method for measuring the friction of a single fiber on a bundle of similar fibers. Essentially, their method involved placing a hair, equally weighted on both ends, over a revolving mandrel whose surface was covered with the reference material. The weight which tends to go downward because of the rotation of the mandrel was supported by a torsion balance arm. The frictional coefficient was calculated by knowing the force which would keep the balance arm in an equilibrium position while the mandrel was revolving at a particular uniform velocity. To determine static friction, the mandrel was kept stationary, and the torsion balance arm was adjusted until the weight it was supporting started to move upward. Modifications of the method were given for running more hairs simultaneously to provide better average values. To determine hair-on-comb friction, the mandrels were made of comb material. These investigators found that the following factors affected the experiments: if rubbing is with or against the grain of the cuticle scales; the loads used; the mandrel velocity; the nature of the rubbing surface—which in the case of hair in turn is affected by the humidity, the nature of the particular hair, and the presence of adsorbed materials.

Microscopic techniques are not only useful for basic study of hair structure. That quantitative microscopic techniques can be applied to toiletry research and development work was pointed out by Bartels (124). As pointed out previously, quantitative aspects are often important in the area of product claim support, an area in which there often is an urgent need for numbers. Bartels used and suggested the use of microspectrophotometry for measuring penetration and changes in reflectivity; the use of phase contrast microscopy, where light absorbing compounds are not the key but differences in refractive index are, for the visualization of different reflectivities of differently colored hair; the use of interference microscopy for obtaining more detailed profiles of surfaces. He also employed polarized light and fluorescence microscopy. Such techniques are applicable to the examination of hair and skin before and after treatment and warrant continued investigation.

IRRITATION POTENTIAL TESTING

One phase of product testing not concerned with efficacy but with side effects of products concerns irritation or possible irritation which the product may impart to its user. The concept here is the one familar to pharmacy; the product must balance the "good" *versus* the "bad," just as side effects must be balanced against efficacy in drug products. Toiletry products from which effects are desired also can have side effects, and these are generally manifested as irritation. It is not the aim of this section to expand at length on this auxiliary but important phase of product testing. However, since this area is an ever-present factor when the formulator chooses his ingredients, it bears some mention.

Skin irritation is generally checked for in one of two ways. The formulations are either put in contact for various time periods with the skin of men or animals, or else a so-called repeat insult technique or one of its variations, such as the exaggerated use test, is used. Such tests demonstrate not only primary irritation but also bring to light the fatiguing phenomenon wherein the skin reacts due to a summation of insults of a subthreshold intensity. Interpretation of results most often brings into play two concepts. The results may be diagnostic, that is, apply only to the individual tested, or be prophetic; again, it could be prophetic for the individual or for the larger group. Obviously, the latter is the goal one desires, as it is mandatory that one create a formulation which will be much less irritating to the vast majority of users than the preparations apparently used by the Venus de Milo. The goal of the tests is to realistically assess the potential danger associated with the product.

Studies designed to uncover sensitization potential or systemic toxicity will not be discussed here. Often these possibilities can be ruled out by a knowledge of the past history of the use of the formulation's ingredients. Of course, if such toxicity cannot be ruled out, such tests must also be run.

Draize *et al.* (125), recognizing the importance of irritation potential testing, pointed out that it is imperative that the inevitable qualitative observation of physiological effects be convertible to reasonably quantitative objective measurements which should be subject to arithmetical interpretation. They applied the principle of assigning numerical values to physiological phenomena, as was done by others in attempts to measure injuries to rabbit eyes. Depending on the type of toxicity tests being run, they used

rubber sleeves or wire mesh screens to hold the agents under test in contact with a shaven area of the test animal; they applied daily relatively large amounts of products; or alternatively, they used patch test techniques. They were able to score these tests numerically. More will be said later about this type of work.

Parenthetically, Henderson and Riley (126) discussed statistical facets of patch testing techniques wherein the rate of positive reactions to be expected in the population could be computed, and Knudsen (127), conversely, calculated the probability of finding no reactors, one reactor, and more than one reactor in groups of various sizes when the rate of positive reactions in the population is known.

Shelanski and Shelanski (128) described a new technique of human patch testing which is a variation of the repeated insult method. Their test was better designed and was shown to be more capable than some other methods of uncovering fatiguing substances. The technique consisted of two phases. During the first, humans received material under a patch for 24 hr., after which the patch was removed and the skin reaction graded. The skin then is allowed to recuperate for 24 hr. This cycle is repeated serially for 15 applications in 30 days with grading after each patch is removed. The second phase begins after the 30-day period after the skin is allowed to recuperate for 2 to 3 weeks. The material is then reapplied for 48 hr. after which grading takes place.

It is of interest that Schwartz (129, 130) also reported a patch test procedure for evaluating sensitizing ability. Schwartz described the basis of much of the present standard basic techniques of prophetic patch testing. He studied the dermatitis caused by the resin finishes of fabrics; the U. S. Public Health Service also was interested in the technique to determine the safety of nylon garments.

Another useful and interesting technique is that of Kligman (131). This method employs an occlusive patch test technique. The patches are firmly affixed to the skin so that variables such as leaky patches or other means of material loss are eliminated; one cannot, however, work with nonaqueous volatile solvents. The basic procedure is that the materials or a solution of the materials are put under patches and affixed to each of 10 people; each person is able to bear about six different preparations. These 10 people are observed for 10 days; at each 24-hr. interval, the skin is inspected for any observable sign of irritation. The data then might appear as illustrated in Table I.

TABLE I.—NUMBER OF PEOPLE[a] WITH OBSERVABLE IRRITATION RESPONSE AT DAY INDICATED WITH PREPARATION INDICATED

	Prepn. Under Test					
Day	*A*	*B*	*C*	*D*	*E*	*F*
1	0	0	0	0	0	0
2	0	0	0	0	0	3
3	0	0	0	0	2	5
4	0	0	1	2	3	7
5	0	0	1	4	5	8
6	0	0	3	4	6	9
7	0	2	4	5	7	10
8	0	3	5	6	9	10
9	1	3	6	7	9	10
10	2	4	6	7	10	10

[a] Total people = 10.

By way of explanation, we observe that the following happened with preparation *C*. The first 3 days none of the 10 people showed signs of irritation; on the fourth day, one person did; on the fifth day, the same person, of course, would still be counted as showing signs of irritation, even though no other people did. On the sixth day, two more people (that is, a total of three now) showed signs of irritation, etc., accumulatively, as shown in the table, until on the tenth day, six people responded and four did not. The results also may be expressed in graphical form. Obviously, in the example the preparations increase in their ability to cause irritation under the test conditions as one goes from *A* through *F*. As with all tests, a reference standard (preferably a commercial preparation *of the same product class*) also should be run so that one has some basis upon which to judge the materials being tested. One notes that the materials *A* to *F* could represent different concentrations of the same ingredient *or* different ingredients in the same or different concentrations. In the latter case, the resulting data also could be expressed by plotting the concentration of a substance *versus* the number of people responding on any one day; this would permit a relative evaluation of different materials as compared with each other.

With regard to patch testing, Osbourn and Tusing (132) presented a technique which facilitated multiple patch testing by employing a single elastic bandage containing multiple gauze patches. We may note also that Moynahan (133) has written a review of the patch test as it is applied to the diagnosis and prevention of cosmetic dermatitis.

Information concerning techniques of testing for potential irritancy from U. S. Government sources is also of interest. The staff of the Division of Pharmacology, Food and Drug Administration, published in 1959 (134) a book containing much information on the appraisal of

the safety of chemicals in foods, drugs, and cosmetics. In it special attention was given by Draize to the subject of dermal toxicity. He suggested that primary irritation (reaction upon initial contact) may be measured by a patch test technique carried out on the abraded and intact skin of at least six clipped albino rabbits. Approximately 0.5 ml. (liquids) or 0.5 Gm. (solids) is placed under 1-in. patches and kept in place for 24 hr. by wrapping rubberized cloth or an equivalent around the immobilized animal. After exposure, the reactions are scored on a 0–4 scale with respect to two sets of criteria: erythema-eschar and edema formation. Scoring is done also after 72 hr. Although the original language is not completely explicit, what is done is that the erythema and edema scores from both the 24- and 72-hr. examinations are added and averaged with the scores for intact and abraded skin being averaged separately; then the two averages are added. This sum (8 is the maximum) is referred to as the primary irritation index. Primary irritation indexes of 0–2 indicate mild irritation potential, 2–6 moderate, over 6 severe.

Although antiperspirants, deodorants, and hair grooms obviously are not intended to be applied so that they will reach the eyes of users, this certainly can happen, especially with the last-mentioned group; therefore, eye studies are also advisable. Albino rabbits are used for eye mucosa irritation studies, Draize (134) recommending nine subjects. About 0.1 ml. of the material to be tested is instilled in one eye, the other eye serving as a control. The first three rabbits do not have their treated eyes washed; the second set of three have their eyes rinsed with 20 ml. of lukewarm water 2 sec. after instillation of the test material; the last three have their eyes flushed 4 sec. after instillation. Ocular reactions are read at 24, 48, and 72 hr., and after 4 and 7 days. A scoring system which weights the effects observed on the cornea, iris, and conjunctivae has been developed. In essence, however, formulations which elicit the development of corneal and iris lesions which do not clear by the seventh day are considered to be severe eye irritants. Incidentally, Kay and Calandra (135) discussed the problem of scoring eye irritation tests in some detail and pointed out that there is no easy solution to the problem of obtaining a totally adequate numerical system.

Even though most foods and cosmetics are exempt from the hazardous substances labeling act, it is interesting to note the carrying over of the government work cited into the Code of Federal Regulations. These regulations, in the sections which make provisions pertaining to hazardous substances, explicitly define both primary and eye irritants (136) and describe methods (137) very similar to those of Draize mentioned above.

Eye test regulations have been amended recently, and it may be appropriate to review them; notification was made by publication in the Federal Register (138). The former official eye test involved essentially using six rabbits, placing 0.1 ml. of material in one eye of each and allowing the other eye to serve as a control, not flushing the eye, and then examining the rabbits for the presence of ocular reactions after 24, 48, and 72 hr. A positive reaction was defined as the presence of any opacity or ulceration of the cornea, inflammation of the iris, partial conjunctivitis, or swelling and partial eversion of the eye lids. The new rules provide a more detailed description of how the test should be run. The amendments make the following changes. Formerly, the eye could be examined either with the unaided eye or with the aid of a hand slit lamp. The new rules require the reading of the eye reactions to be made with a hand slit lamp, a binocular loupe, or with "other expert means." Also, an additional optional test consisting of using a fluorescein disclosing solution to highlight corneal damage is suggested. Another change in the test procedure concerns the number of rabbits used. Instead of the former test's six rabbits and with the test being positive upon the appearance of any reaction in any of the six, the new test starts with six rabbits and is considered to be positive if four or more of the rabbits react, negative if only one does. If, however, only two or three out of the first six react, the test is repeated with six more rabbits. If three or more out of the second set of six react, the result is positive; if only one or two react, the test is repeated for the third time with six more rabbits. If one or more of the third set react, the test is positive. The Superintendent of Documents sells an "Illustrated Guide for Grading Eye Irritation by Hazardous Substances" to assist in interpreting test results. The new regulations became effective October 17, 1964.

Finally, with respect to formulatory aspects of irritation potential, the technique of decreasing irritancy by inactivating the active ingredient should not be neglected. Obviously, certain agents may be added to complex the offender or to simply envelop it or coat the skin to prevent its contacting this surface. The problem is again one of trying to obtain only desired effects and to eliminate side reactions—something which, as in

pharmaceutical technology, is not always readily attained. Of course, in the present context, the hope is that the inactivated ingredient will be able to maintain some useful equilibrium concentration and not be completely inactive. Some cases which actually appear to have achieved this will be cited.

Shelanski *et al.* (139), using the observation that PVP is a good complexing agent, showed that the toxicity of PVP–iodine *versus* iodine alone is cut by a factor of ten. It also was noted that PVP reduces the toxicity of mercury, nicotine, and cyanides. Although such complexing tendencies may help one to strike a balance between effectiveness and toxicity, it is possible that effectiveness will be reduced in most cases if the therapeutic ratio is not appropriate. Burnette (140) reviewed the world literature and also recorded that, among its other physiological properties, PVP reduced the toxicity of cyanides, mercury, arsenic, iodine, and also toxins produced in infections such as tetanus, diphtheria, botulism, and bovine mastitis.

Another example of utilizing such complexing mechanisms to reduce toxicity or irritation potential is that of Libby (141), who has found that cationic surface-active agents will, in a shampoo composition, have reduced ophthalmic irritancy when combined with certain anionic cycloimidine derivatives. It is difficult in this case, however, to monitor the activity of the cations to determine if it has been lost.

Traub (142) in a study of the irritation potential of hexachlorophene indicated negative results when the material was used for 48 hr. in a closed patch test at concentrations of 0.5% and 1.0% in petrolatum. Looking at it the other way, it appears that all activity has been lost. One notes that the vehicle has not been considered, and the result (that the material is not irritating) is invalid; as Kligman (23) said about another published report, this is also a "significant contribution to the literature of error and fallacy."

CONCLUSION

When viewed in the whole milieu of product development technology, the field of toiletries has, and deserves, its own special niche. The best work in this field can be done when the pertinent basic physiology and various facets of all the chemical disciplines are understood and brought into play. It has been the purpose of this article to illustrate the truth of these statements, taking as examples deodorant, antiperspirant, and hair control products.

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