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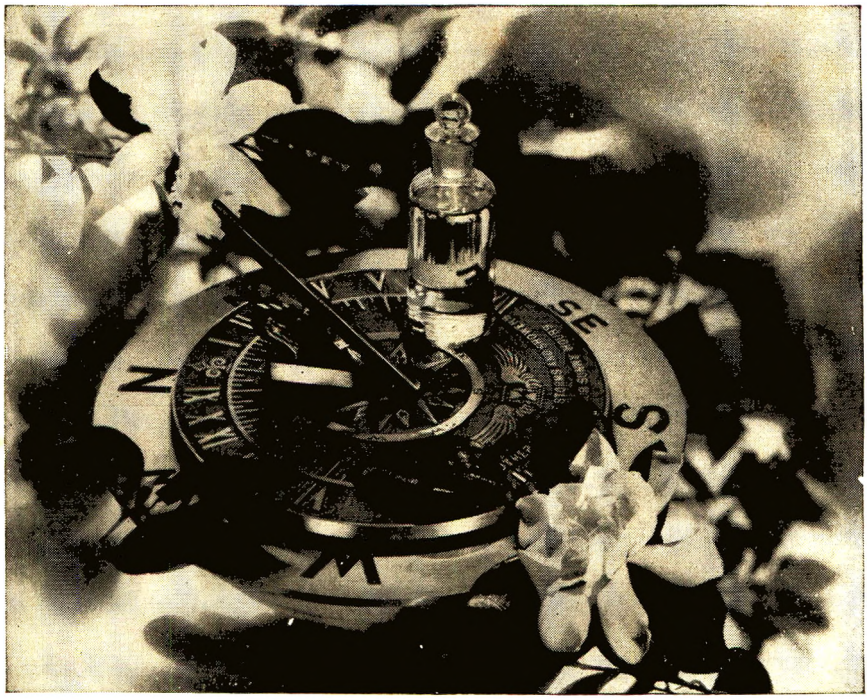

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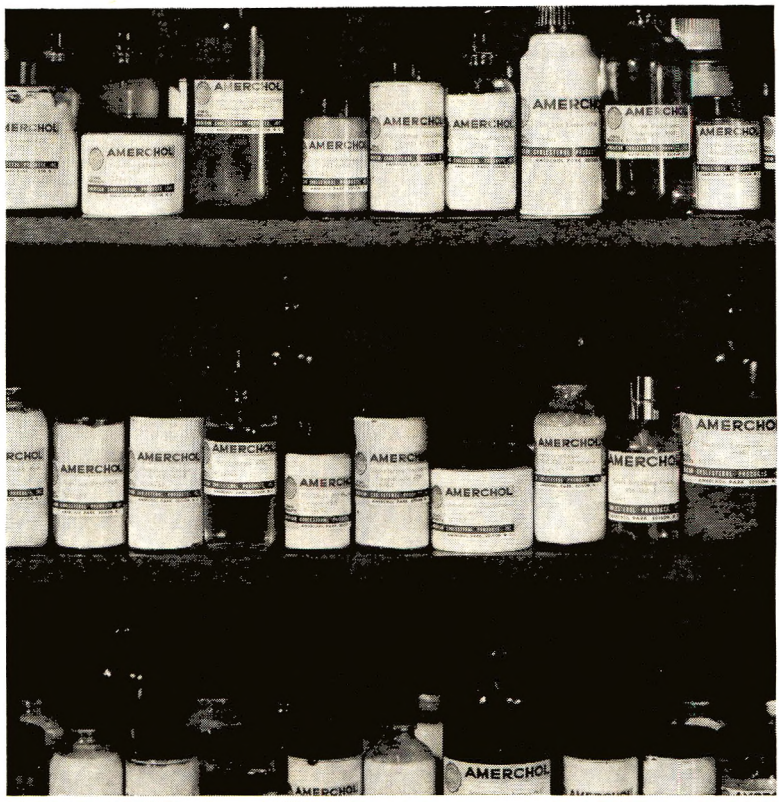

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TORONTO MONTREAL

VARIATIONS IN AXILLARY ODOR

By Najib Shehadeh, M.D.
and Albert M. Kligman, M.D., Ph.D.*

Some persons, and some races, emit an axillary odor which is a good deal stronger than that of others. The cause of these differences is the subject of this inquiry.

Method

The study was designed to contrast the extremely odorous with the practically nonodorous, as determined by experienced "smellers." Since odor results from bacterial decomposition of apocrine sweat, the factors bearing upon this result were analyzed separately as follows:

a. Bacterial Density. The odor might be proportionate to the number of organisms available to metabolize apocrine secretion. Bacterial counts were made using the previously described "scrubbing-machine" (1). The vault of each axilla was sampled and the results averaged.

b. Eccrine Sweat. Water, through its hydrating effect on the horny layer, is an important factor in controlling the number of surface organisms (2). The dry regions have the lowest counts. The sweating capacity of the eccrine glands was measured by absorbing the sweat of each axilla into nonwoven cotton pads (Webril, Curity). Pads, 8 × 4 in., were folded once and inserted into the axilla. The subject kept his arms close to his side during a 30 minute exposure in a chamber of 100% relative humidity and 130°F. Because of the crudity of the method, measurements were made daily for five days and averaged.

Hairiness

There were two reasons for examining the amount of axillary hair. (1) The more hair, the more surface to support bacteria, as well as increased adsorption of apocrine sweat and its derived odors. (2) Since each hair follicle has one sebaceous and one apocrine gland to form the apo-pilosebaceous unit, the size of the apocrine apparatus might parallel the size of the hair. A hairy axilla might then indicate an abundance of apocrine sweat.

* Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia 4, Pa.

Hairiness was estimated visually on an arbitrary scale of 1 to 5, taking into account the total bulk of the hair, which is, of course, dependent on hair density and length.

Apocrine Gland Volume

This was microscopically estimated in thick celloidin imbedded, anthracene blue stained specimens. An arbitrary scale of 1 to 5 was used to estimate the number of coils making up the secretory portion of the gland. This is a crude but satisfactory method, if the differences are large.

Pharmacologic Stimulation

0.1 ml. of 1:10,000 epinephrine hydrochloride and 0.1 ml. of 1:10,000 Mecholyl were injected intradermally to visualize the number and size of the apocrine droplets.

Subjects

The subjects were 16 adult, Negro, male, volunteer prisoners. Eight were maximally odoriferous and eight scarcely so (none used deodorants).

Results

The attempt to estimate the volume of apocrine secretion by injection of cholinergic and adrenergic chemo-mediators proved futile. In these subjects, as well as many others, only a few tiny apocrine droplets, or none at all, appeared following intradermal injection. It is only the rare individual in whom enough sweat can be delivered by such means to make quantitative estimation possible.

As regards the other factors studied, a summation is presented in Table I.

Table I—Weakly *vs.* Strongly Odorous Subjects

Subject	Odor	Bacterial Count, millions/sq. cm.	Sweat, gm.	Hairiness, 1–5	Apocrine Gland Volume, 1–5
1	Maximum	3.1	0.61	2	4
2	Maximum	3.6	2.70	1	
3	Maximum	3.1	0.95	4	5
4	Maximum	4.9	2.98	3	
5	Maximum	4.5	2.21	2	4
6	Maximum	2.7	2.57	3	4
7	Maximum	3.2	3.43	5	5
8	Maximum	9.0	4.87	2	
Average		4.2	2.54	2.8	4.4
1	Minimum	6.1	2.00	5	2
2	Minimum	6.4	4.30	2	
3	Minimum	3.5	3.41	2	3
4	Minimum	4.0	5.18	3	2
5	Minimum	6.8	3.77	2	
6	Minimum	2.8	3.35	4	2
7	Minimum	4.8	2.09	1	
8	Minimum	2.6	3.02	3	3
Average		4.5	3.31	2.8	2.4

Discrimination between the extremely and mildly odorous subjects was obtained only in respect to one parameter, apocrine gland volume. The secretory portion of the glands of highly odorous persons is considerably larger. Even in unstained, fresh biopsy specimens, their bulk occupies most of the mass of the upper subcutaneous tissue. This size difference is immediately apparent in stained thick sections. Odorousness is independent of bacterial density, hairiness and eccrine sweat capacity.

Comment

In vitro, a single droplet can be shown to generate a remarkably potent odor in the presence of gram positive resident organisms. The actual volume of apocrine sweat produced daily is minuscular and immeasurably smaller than the potential for eccrine sweating. Since hairiness is a function of follicular density and is nonvariant with respect to odor, it seems certain that it is not the number of apocrine glands but their size which is decisive. It is assumed that larger glands produce more sweat. Though apocrine secretion is mainly a vestigial function in man, who at best secretes very small quantities, it would appear that the slightly greater amount produced by subjects with larger glands is sufficient to account for greatly increased odorousness. An alternative but improbable explanation is a qualitative difference in the composition of apocrine sweat.

In our experience, the Negro has a stronger axillary odor than the white; this feature correlates well with larger apocrine glands. The statement has truth only with regard to the average since individual differences may encompass the whole range as we have demonstrated in our selected Negro subjects. The reputed smallness of the apocrine glands of the Japanese would account for their relative nonodorousness.

Summary

Intensely and mildly odorous subjects were compared with respect to axillary hairiness, eccrine sweating, bacterial density and apocrine gland size. The only difference was the considerably greater secretory bulk of the apocrine glands of the strongly odorous persons.

Assuming that larger glands make more sweat, it was concluded that it is this anatomical factor which accounts for the greater odorousness of some subjects and some racial groups.

(Received August 2, 1963)

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A REVIEW OF SOME RECENT FINDINGS ON RADIATION-INDUCED TANNING OF MAMMALIAN SKIN*

By WALTER C. QUEVEDO, JR., PH.D.†

Presented May 8, 1963, Semi-Annual Scientific Meeting of the Society of Cosmetic Chemists Held in Joint Sponsorship with the American Medical Association Committee on Cosmetics

When mammals are exposed to ultraviolet light (UV), the epidermis of their skin becomes darker (tanned) and thicker (1–13). The tanning is caused first by a darkening of pre-existing melanin granules and later by the biogenesis of new melanin within melanocytes of the dermoepidermal junction. The thickening of the epidermis is achieved by increased proliferation of the malpighian cells with a resulting enlargement of the stratum corneum. The intensity of radiation-induced darkening is based, in the main, on the formation of new melanin granules within melanocytes and their accumulation within the increased population of malpighian cells. The transfer of pigment granules from melanocytes to malpighian cells has been described as "cytocrine activity," implying that there is an active secretion of melanin granules (14); however, the exact mechanism of this transfer is not clear. It has recently been suggested that malpighian cells acquire melanin granules by "pinching off" parts of the pigment-bearing dendritic processes of melanocytes (15–18). As a consequence, the rate of melanin synthesis within the melanocytes may be regulated by a "feedback" mechanism of control being dependent on the rate at which melanin granules are removed by malpighian cells (18). The UV-induced proliferation of malpighian cells, by providing increased numbers of vehicles for the removal of melanin, may play some role in stimulating melanogenic activity within melanocytes. This view of melanogenesis stresses the interdependence of melanocytes and malpighian cells (12, 19) and has given rise to the concept of an *epidermal melanin unit* (18). Each *epidermal melanin unit* consists of an epidermal melanocyte and a constellation of malpighian cells with which it is associated.

* Some of the work described herein was supported by PHS Research Grant # CA-06097-02 from the National Cancer Institute and PHS Training Grant #2G-582(C1) (William Montagna, Director) from the Division of General Medical Sciences, United States Public Health Service.

† Biology Dept., Brown University, Providence 12, R. I.

Although it is now clear that there is an intimate association of melanocytes and malpighian cells in the evolution of radiation-induced hyperpigmentation, the general mechanisms that regulate this phenomenon remain largely uncharacterized. Of particular significance are the roles that hereditary and hormonal factors may play in determining the "tanning potential" of mammalian skin. It is the purpose of the present report to review briefly some contributions of research on laboratory animals leading toward an understanding of this complex problem.*

Tanning in Mice

The value of the laboratory mouse for studies on radiation-induced tanning first became evident when hyperpigmentation was observed in the extremities of pigmented mice exposed daily to gamma-rays for the duration of life (9). Although all of the extremities of the gamma-irradiated mice darkened, the plantar surfaces of the hind feet were the most reliable sites for evaluating pigment increase. Similar observations were made on mice treated with x-rays or ultraviolet light (Fig. 1) (9, 11). An arbitrary grading system was devised for subjectively measuring the rate of tanning (Fig. 2). Within limits, the plantar skin acted as a "biological dosimeter" wherein the rate of tanning was influenced by the daily dose-rate of radiation (9). At the cellular level, the hyperpigmentation elicited by x-, gamma-, and UV-radiations resulted from increased melanogenic activity within individual epidermal melanocytes, increased numbers of melanogenic melanocytes, and increased deposition of melanin granules within malpighian cells (Fig. 3). Direct exposure to the radiations was necessary to induce tanning within the skin; continued treatments were necessary to maintain it (Fig. 1) (9, 11, 12).

Hormones and Tanning

In an attempt to characterize the mechanisms which regulate the tanning process, hormonal effects were studied in C57BL (black) and LAF_1 (brown) mice receiving daily total body irradiation with 97 r/day or 125 r/day of gamma-rays (11). Intact, gamma-irradiated C57BL and LAF_1 mice achieved the maximum +++ grade of tanning in the plantar skin between the nineteenth and twenty-fifth day of treatment. Orchidectomy and oophorectomy did not alter the tanning response. Similarly, adrenalectomized mice, although showing higher mortality on exposure to gamma-rays, darkened at the same rate as the intact control mice. Daily treatment of intact mice with high doses of adrenocorticotropic hormone (1 to 4 U.S.P. units/day) also failed to modify the tanning process.

* The main emphasis of this paper is on work performed by the author and his associates. Although presenting a cross-sectional view of the current knowledge of tanning in mammals, it is not intended to be an exhaustive treatment of this subject.

Figure 1.—Hind feet of a pigmented mouse of the L strain after 16 daily treatments with UV. Note the intense tanning (+++ grade) in the irradiated foot (arrow). The slight amount of residual pigmentation in the shielded foot did not increase during the period of treatment. Reproduced from Quevedo and Smith (12), with permission of The New York Academy of Sciences.

Subsequently, the general effect of pituitary hormones was tested in hypophysectomized juvenile NIH black rats. The plantar skins of the intact and hypophysectomized rats darkened markedly on repeated x-irradiation and were indistinguishable in their intensity of tanning (11). Collectively, the findings on animals irradiated following surgical removal of specific endocrine glands, when added to those of the shielding studies, stressed the local nature of mechanisms controlling the tanning response within murine skin.

Nonetheless, daily treatments with cortisone did inhibit radiation-induced tanning when administered in sufficient quantities (2.5 to 6.0 mg./day) to intact mice (11). Similarly, daily treatments with 1.0 mg. of diethylstilbestrol prevented significant tanning in gamma-irradiated mice. There was a slight increase in the number of melanogenic melanocytes in the skin of irradiated mice treated with cortisone or diethylstilbestrol, but the numbers were dramatically less than those of control mice,

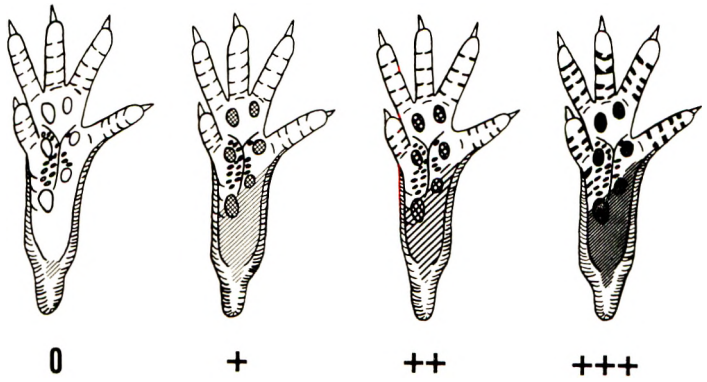

Figure 2.—Grades of tanning in the feet of irradiated mice. The grades range from 0, for no radiation-induced darkening, to +++, characterized by an intense darkening of the general plantar surface and the presence of darkly pigmented bands on the toes.

and little melanin was found within malpighian cells. This finding indicates that cortisone and diethylstilbestrol in the quantities employed did not completely prevent epidermal melanocytes from responding to radiant energy (11). In view of the failure of hypophysectomy to influence tanning, it is probable that cortisone and diethylstilbestrol inhibited darkening by a direct rather than pituitary-mediated action on the melanocytes. At present, closer attention is being given to the identification of hormonal effects at the cellular level that may not be reflected in the gross tanning of irradiated skin.

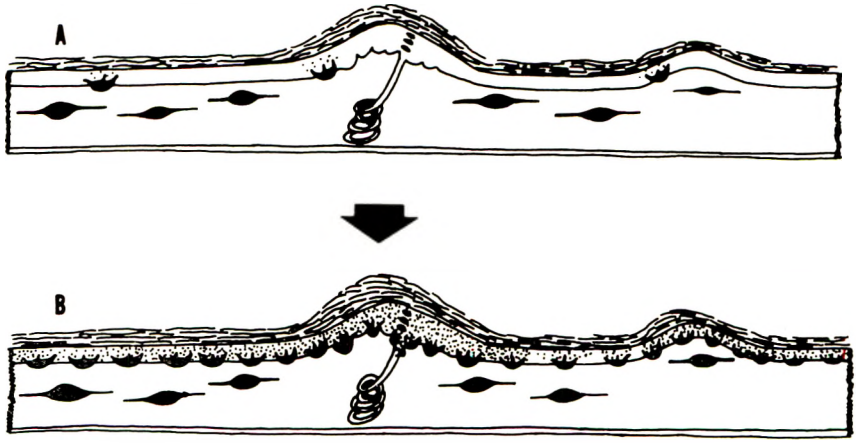

Figure 3.—Diagram of plantar skin sectioned longitudinally. (A) Non-irradiated: Only a few melanotic melanocytes are present at the dermoepidermal junction, and there is little pigment within the epidermis. (B) Irradiated: A marked increase in melanotic epidermal melanocytes and in melanin granules within the epidermis accounts for the tanning shown in Figure 1.

Genes and Tanning

Hereditary mechanisms influence every phase of melanocyte form and function. The action of genes on pigmentation has been particularly well studied with reference to the coat color of mice (20–27). Utilizing this body of information, the role of genes in regulating the "tanning potential" of skin was examined in mice of 13 different inbred strains and three special stocks selected on the basis of characteristic differences in hair coloration (12). The problem was to determine the extent to which mice clearly differing in their qualitative and quantitative mechanisms for melanin synthesis also differed in their ability to tan. More specifically, what differences in intra- and inter-cellular events accounted for gross differences in radiation-induced darkening of the skin, and how might such events be a manifestation of underlying genetic control? From these studies it became evident that specific genes regulate the "tanning potential" of irradiated mammalian skin by influences on melanocyte morphology, melanocyte distribution, melanocyte activation, the color and size of pigment granules and the total amount of pigment synthesized by melanocytes. Each melanocyte synthesizes melanin pigment in quantities and with qualities specified not only by its own genetic machinery but also in some cases by the cellular community of which it forms a part (12, 20, 21, 22). The magnitude of gross tanning elicited by UV is predetermined by programing mechanisms which regulate the melanogenic performance of melanocytes and the accumulation of melanin within malpighian cells (12). Although genetic effects on the mobilization of malpighian cells were not examined, such mechanisms no doubt are of importance in this phase of the tanning process.

Usually, mice with the darkest hair coloration showed the most intense tanning response to UV (12). In mice achieving a +++ grade of tanning, there was a striking increase in the number of melanogenic epidermal melanocytes within the plantar skin (Fig. 3). In some cases the number of melanocytes in a given area of irradiated plantar skin was 10 to 30 times greater than that found in nonirradiated skin. For example, in C57BL mice there were approximately eighty melanotic melanocytes/mm.^{2} in nonirradiated plantar skin and 1100 melanotic melanocytes/mm.^{2} in irradiated skin. In addition, large numbers of melanin granules were located within the irradiated malpighian cells. Although a similar increase in melanocytes usually was noted within the irradiated skin of mice exhibiting a + to ++ tan, the color of the pigment granules and in some cases the numbers of pigment granules within the epidermis were insufficient to cause a gross grade of +++.

In those mice that failed to show any evidence of UV-induced tanning, several different mechanisms appeared to be operative. No evidence of melanin synthesis was found in albino mice treated with UV. Mice of

two different strains characterized by a light brown coat color (IPBR and PBR) also failed to tan (12). However, examination of their skin showed a striking increase in melanotic melanocytes at the dermoepidermal junction. These melanocytes, although clearly melanotic, produced only a few melanin granules, which were small in size and light in color. Little pigment was found outside of the irradiated melanocytes. It is possible that the melanogenic activity (manufacture of melanosomes*) of the melanocytes did not reach a level high enough to permit the release of melanin granules to malpighian cells. The absence of tanning appeared to be associated with the gene-regulated restricted capacity for melanogenesis which persisted in spite of repeated exposures to UV. Thus, the judicious use of genetically characterized mice permitted both an identification of the critical stages in the development of tan and the specific sites of gene action which accounted for variability in the tanning response.

Although the melanocyte system of the glabrous plantar skin has been the major target for study, the melanocyte system in hairy skin has also been examined (10). The significance of such a study lies in the fact that there are striking differences in the architecture of the epidermis of hairy and glabrous skin surfaces. One might predict that the morphological differences reflect underlying biochemical differences and accordingly that the epidermal melanocytes of these regions would differ in their responses to UV. However, in spite of the striking anatomical differences, it was demonstrated that the melanocytes of hairy and glabrous skin respond to UV in an essentially identical manner. In genotypes of mice showing intense tanning of the plantar skin, there was a correspondingly intense darkening of the irradiated (depilated) general body skin. Whereas melanotic epidermal melanocytes were rarely encountered in the hairy skin of nonirradiated mice, irradiation produced a marked increase in their number. As in the plantar skin, the activated melanocytes often discharged significant amounts of melanin to malpighian cells. With few exceptions, in genotypes of mice showing little to no tanning in the plantar skin, there was a similar failure of the hairy skin to darken on exposure to UV. Thus, the epidermal melanocyte populations of hairy and glabrous skin appear to share a similar developmental fate.

Pigment Cell Populations During Tanning

What is the source of the increased numbers of melanogenic melanocytes found in murine skin after UV-irradiation? As yet no certain answer can be given to this question. The increased number of melanotic melanocytes might simply reflect the progressive activation of melanogenic activity

* Recently, the term "melanosome" has been widely used to distinguish developing melanin granules from the fully mature forms. Some authors would designate all melanin inclusions of melanocytes as melanosomes, regardless of their developmental status.

within many nonpigmented melanocytes. To test this idea, an attempt was made to identify amelanotic melanocytes* within the plantar skin. The generally accepted methods (osmium iodide and brilliant cresyl blue) for staining amelanotic melanocytes revealed reactive cells at the dermoepidermal junction; as yet, no completely satisfactory estimates have been made of their numbers. To test the possibility that melanocyte proliferation might also contribute to the increased numbers of melanotic melanocytes, mice were exposed to UV and injected with colcemid five hours before they were sacrificed on the sixth to twelfth day of irradiation. This was the period when melanotic melanocytes were found to be undergoing the most rapid change in numbers. The treatment with colcemid arrested mitosis at the metaphase stage, permitting a ready identification of division within melanocytes. Preliminary studies indicate that melanocytes were stimulated to divide in response to UV. Therefore, it is quite possible that the tanning of murine skin is related both to the activation of nonpigmented melanocytes and to an absolute increase in the numbers of melanocytes. Recently, Snell (13) found a marked increase in the melanotic epidermal melanocytes within the irradiated skin of pigmented guinea pigs but did not observe a proliferation of melanocytes.

Species Differences in Tanning

Somewhat different mechanisms may account for tanning in the few mammals which have been studied so far. All of the epidermal melanocytes in human skin are thought to react to the DOPA-reagent (a buffered solution of β-(3,4-dihydroxyphenyl)-L-alanine) becoming dark, owing to their capacity for converting DOPA to melanin (28). Although there is not complete agreement (29, 30), it is generally stated that human melanocytes do not increase in number following treatments with UV (28, 31–33). In fact, a reduction in the number of DOPA-reactive melanocytes has been reported to occur in irradiated human skin (32). In the mouse (12) and guinea pig (13), the dramatic increase in numbers of melanogenic melanocytes is a significant feature of the tanning process.

Albinism is characteristically found in humans and rodents, as well as in many other animals. UV fails entirely to elicit melanogenesis in albino mice (12); the melanocytes in irradiated and nonirradiated skin neither produce melanin granules nor react with DOPA-reagent. In contrast, the melanocytes of human albinos are DOPA-positive, and exposure to UV intensifies the DOPA-reactivity of these melanocytes (34, 35). Recent studies indicate that the melanocytes of albino mice produce precursor pigment granules (premelanosomes) which do not darken, owing

* Strictly speaking, the nature of the epidermal amelanotic melanocyte is not known. If it is truly embryonic in character, i.e., fully "undifferentiated," it might more properly be designated as a melanoblast.

to the absence of a competent tyrosinase system (36, 37). In contrast, the melanocytes of human albinos are capable of synthesizing melanosomes with active tyrosinase, albeit reduced in amount (34, 35).

Under the conditions of the experiments described above, it would appear that radiation-induced tanning in the mouse is largely a local phenomenon. That is to say, the primary mechanisms regulating the response of epidermal melanocytes to radiations reside within the skin. Nonetheless, a wealth of experimental and clinical data clearly indicates that hormones also regulate many phases of mammalian pigment cell function (38, 39). In the mouse and rat, it is possible that hormones and radiations exercise independent actions on the peripheral mechanism of pigmentary control. Their interactions may be quite different in other mammalian species, including man (38, 39).

Cellular Interactions During Tanning

The nature of UV damage to the epidermis suggests that the normal stimulus for melanogenesis may originate within malpighian cells and is transferred to melanocytes, resulting in their "activation" (2, 5). The form of this message is obscure. Although epidermal hyperplasia may stimulate the melanogenic activity of melanocytes to a higher level by removing melanin granules at increased rates, it would appear most likely that the primary initiation of melanogenesis requires another message. Since UV has been demonstrated to be absorbed by epidermal nucleoproteins, it is possible that they are in some way associated with the origin of the message which eventually initiates melanin synthesis within the melanocytes of irradiated skin (2). However, other epidermal components have been identified as potential targets for UV absorption and also may be linked to the activation of irradiated melanocytes (2, 3, 5).

Genetic mechanisms, in addition to their more obvious effects on the chemistry and morphology of melanin granules synthesized by melanocytes, may regulate the "tanning potential" of skin by setting limits on the absolute rate of melanin synthesis in response to messages arising from repeated UV trauma. How this is brought about remains to be determined. The genetic regulatory system may act directly within the melanocyte, through its extracellular environment, or by both routes. Considerable insight into the important problem of cellular interactions during tanning will be forthcoming when more information is available on the biochemical nature of cellular changes within irradiated skin.

(Received September 3, 1963)

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THE FUNCTION OF THE ECCRINE SWEAT GLAND*

By Richard L. Dobson, M.D.†

Presented May 8, 1963, Semi-Annual Scientific Meeting of the Society of Cosmetic Chemists Held in Joint Sponsorship with the American Medical Association Committee on Cosmetics

Abstract

The main function of the sweat gland is concerned with temperature regulation, and any salt in the aqueous sweat is wasted. After repeated exposures to a hot environment the sodium content of human eccrine sweat falls. This adaptive process, called acclimatization, involves both structural and functional factors. If acclimatization is prevented by the administration of large amounts of salt, the sodium content of the sweat remains high, and no cellular changes are seen in the gland. On a low salt intake, the rate of sweat sodium excretion falls, and marked cellular changes in both secretory and duct cells are seen. If corticosteroids are given, however, all the features of acclimatization can be produced even in subjects on a high salt intake.

Many aspects of sweat gland function appear paradoxical. Pharmacologically, the eccrine gland responds to cholinergic stimuli, yet it is sympathetically innervated. After denervation the sweat gland is totally unresponsive, although it remains morphologically intact indefinitely. Physiologically, on first exposure to a hot environment, the eccrine sweat gland wastes salt, but it is this very wastage which leads to a series of events culminating in the ability of the gland to conserve sodium. Anatomically, the cells of the sweat gland undergo profound changes during sweating which, in turn, have functional consequences.

These characteristics probably represent manifestations of the unique adaptive processes which the eccrine sweat glands have undergone in man. Most mammals rely on a thick furry coat to protect them from heat. Man in his nakedness no longer is protected by insulation. He, therefore, must depend on evaporation to adapt to a hot environment. This, then, is the main function of the eccrine sweat gland—to produce water for evaporative heat loss. The current concepts of how this is done will be the central theme of this presentation.

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Anatomically, the eccrine sweat gland (Fig. 1) is a fairly simple tubular structure consisting of a single-layered secretory coil and a double-layered duct. The distal duct has a helical configuration within the epidermis which, with the surrounding epidermal cells, has been termed "the epidermal sweat duct unit" (1). The secretory coil is surrounded by a layer of myoepithelial cells, which, although their name implies contractile properties, do not have, on the basis of available evidence, any known function in man.

As has been already mentioned, during profuse thermal sweating, cellular changes occur in both the secretory coil and duct, especially if the salt intake is low (2). It is also known that during sweating changes occur in both the composition of sweat and in the sweat rate (3). With repeated episodes of profuse sweating, the rate of salt excretion gradually falls, reaching minimal levels in a few days. This is a part of the process of acclimatization to heat.

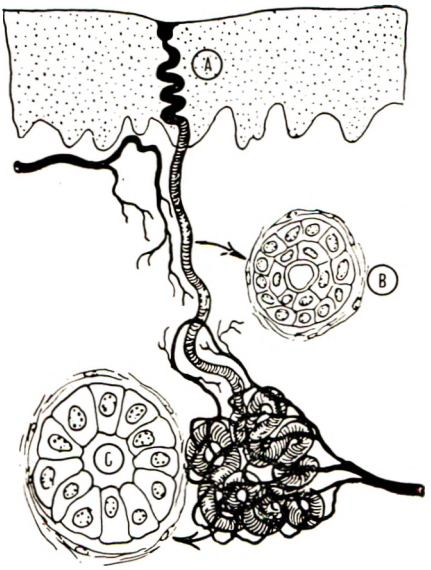

Figure 1.—A diagram of the normal human eccrine sweat gland showing: A. The epidermal sweat duct unit; B. The double-layered duct. C. The single-layered secretory coil.

Considerable insight into the mechanism of function of the sweat gland was obtained by studying the effects of salt intake (4). On a high-salt intake the rate of sodium excretion is high and remains so day after day. With salt deficiency, on the other hand, there is a progressive decline in the daily rate of sodium excretion (Fig. 2). The rate of sweating, however, is not affected by salt intake, there being an initial rise and then a gradual fall during a six-hour exposure to heat (Fig.3). In both cases, furthermore, the pattern of sodium excretion is similar, reaching a maximum at about two hours and then gradually falling (Fig. 4). It is therefore apparent that the rate of sweating and the rate of sodium excretion, regardless of salt intake, are closely correlated and run parallel courses.

Referring again to Fig. 4, it can be seen that the curve can be divided into two parts. During phase I, the secretory phase, sodium excretion rises, resulting in a depletion of body sodium and, since the sweat rate is rising, a loss of water also. This produces a contraction of the extracellular volume. During phase II, the reabsorptive phase, the rate of

sodium excretion progressively falls, as does the sweat rate. As has been so clearly shown by Conn (5), the consequences of phase I result in the production of aldosterone by the adrenal gland. Let us postulate, therefore, that aldosterone facilitates the reabsorption of salt in the sweat duct during phase II by a mechanism similar to that which takes place in the renal tubule. Under these circumstances, sodium will be actively reabsorbed, and water will passively follow because of the osmotic gradient which has been established. Thus the sweat rate and rate of sodium excretion in the sweat are directly correlated.

If this hypothesis is valid, it should be possible to initiate the reabsorptive phase from the onset of sweating by the administration of a potent self-active corticosteroid such as 9α-fluorohydrocortisone (6). When this was done, there was a low constant rate of sodium excretion (Fig. 5). In other words, the reabsorptive phase was active throughout sweating. Although this study was done in men given large amounts of salt, the sweat glands behaved, both functionally and structurally, as though there was salt depletion. This would suggest that the cellular changes observed as a result of profuse sweating are a reflection not of salt intake, *per se*, but rather the amount of metabolic work the gland is required to perform. The lower the rate of sodium excretion the more sodium there is to be reabsorbed by the duct and thus a greater work load.

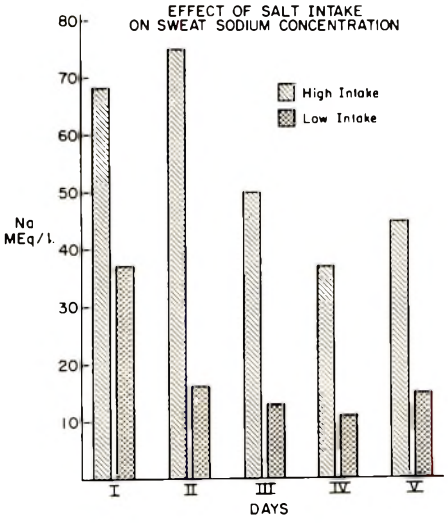

Figure 2.—On a high salt intake sodium excretion remains high. On a low salt intake there is progressive fall in sodium excretion to low levels.

Following this line of reasoning still further it should be possible to block reabsorption of sodium in the duct with a diuretic. When methychlothiazide was given to salt-loaded men, the reabsorptive phase was blocked (Fig. 6). Furthermore, since metabolic work was reduced, no cellular changes in the sweat gland were seen (6). It is important to note, however, that the secretory phase was also blocked by the diuretic, suggesting that the secretory coil also actively transports sodium.

On the basis of this evidence a concept of sweat gland function which takes into account both structure and function can be formulated. This is illustrated in Fig. 7. From a precursor fluid (P. F.) derived from blood

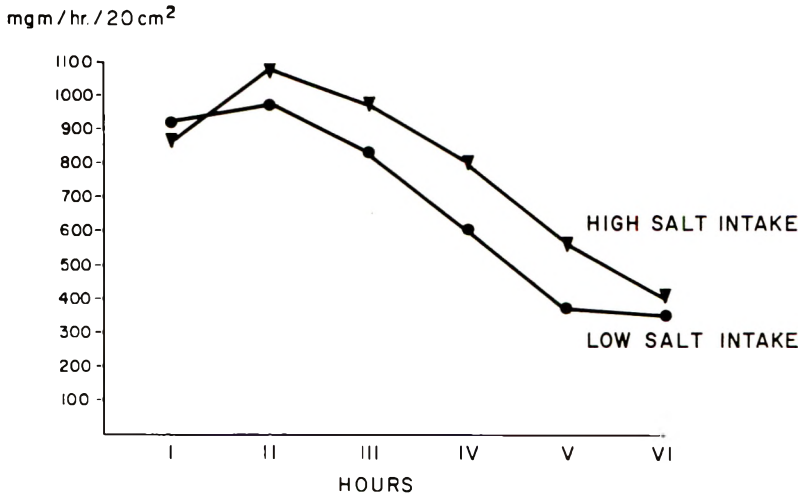

Figure 3.—Salt intake does not affect the sweat rate.

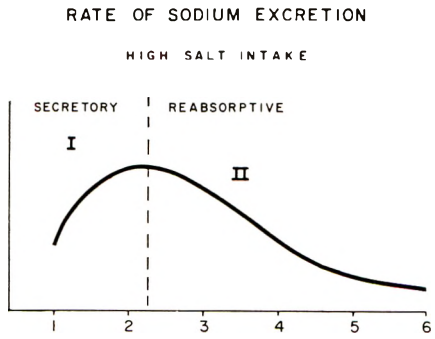

Figure 4.—See text for description.

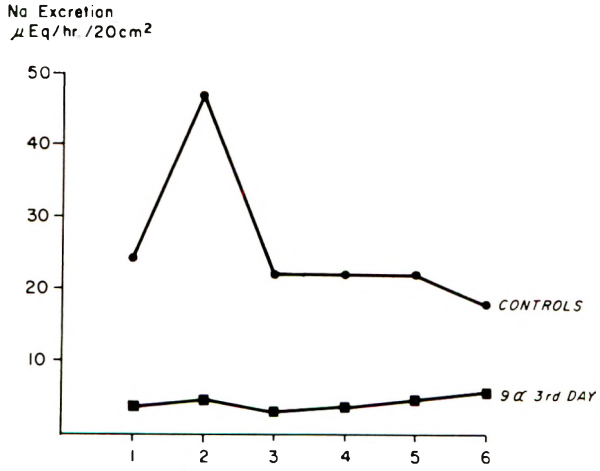

Figure 5.—Effect of 9α-fluorohydrocortisone on the rate of sweat sodium excretion.

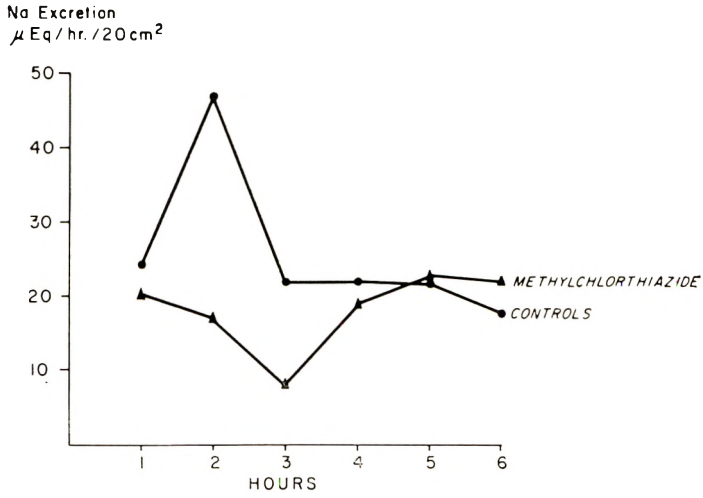

Figure 6.—Effect of a diuretic on the rate of sweat sodium excretion.

the secretory coil (S. C.) actively transports sodium across the secretory cells. With salt-depletion and contraction of the extracellular volume as a result of profuse sweating, aldosterone excretion is increased. This, in turn, facilitates the active reabsorption of sodium from the lumen of the duct across the ductal cells, increasing the concentration of sodium in the tissues outside the duct. To restore osmotic equilibrium, water passively diffuses across the duct into the tissues.

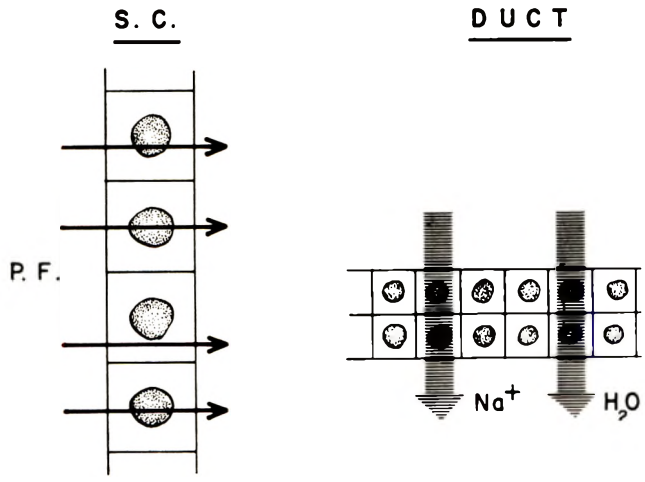

Figure 7.—A hypothetical model of the mechanism of sodium excretion by the sweat gland.

With repeated episodes of profuse sweating persistent changes occur in the secretory cells, presumably rendering them less capable of secreting sodium and thus lessening the work load of the duct which has been shown to have a limited capacity to reabsorb sodium (7). In this way a mechanism is established by which dilute sweat can be produced in amounts sufficient for evaporative heat loss without general salt depletion resulting.

The mechanism of acclimatization to heat therefore involves an adrenal mechanism (aldosterone) as well as structural and functional changes in the eccrine sweat gland. As Conn (5) has so clearly shown, the response of the kidney during acclimatization differs from that of the sweat gland. In both there is an initial decrease in the rate of sodium excretion. After several days, however, urinary sodium increases despite continued high levels of aldosterone. The rate of sodium excretion in the sweat remains low. It seems that the cellular changes which occur in the eccrine secretory cells provide a way of insuring low sweat sodium excretion so that acclimatization persists. The kidney, however, partially escapes from the effects of aldosterone, thus leaving it free to function in its role as the general regulator of salt and water balance.

Summary

The major function of the human eccrine sweat gland is to produce water for evaporative heat loss. Any salt in sweat, therefore, is wasteful. With repeated exposure to a hot environment the output of sodium in sweat gradually falls. This acclimatization is dependent on adrenal cortical factors as well as structural and functional changes in the sweat gland.

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THE STRUCTURE, FUNCTION AND FORMULATION OF TOPICAL SUN SCREENS I. THEORETICAL CONSIDERATIONS

By Saul I. Kreps, Ph.D.*

Presented May 8, 1963, Semi-Annual Scientific Meeting of the Society of Cosmetic Chemists Held in Joint Sponsorship with the American Medical Association Committee on Cosmetics

Abstract

Theoretical considerations of radiation intensity and of the skin's response to incident radiation are discussed. Various properties of sun screening agents, of importance to cosmetic formulators, are mentioned. Among these, the absorption spectrum, absorption through the skin and pharmacological inertness are of particular importance and are discussed in greater detail.

Introduction

The design of a satisfactory suntan preparation involves the interaction of three factors, all of which must be understood before an acceptable result can be achieved. The major purpose of the material is to interpose an ultraviolet-absorbing screen between the skin and radiant energy in sunlight to modify the reaction of the skin to irradiation. The intensity and physiological effects of the energy, the quantitative response of the skin to irradiation, and the ultraviolet-absorbing characteristics of the interposed screen must all be balanced to achieve the desired effect.

Quantitation of Incident Radiation

The sun emits energy in a grossly continuous band throughout the electromagnetic spectrum. Passing through the upper atmosphere, the shorter wavelengths are absorbed by atmospheric components so that at sea level the radiation extends from a cutoff near 290 mμ through the near ultraviolet to the conventional end of the ultraviolet range, which is 400 mμ. The intensity of the radiation varies nonlinearly throughout this range.

The relative response of so-called "normal" Caucasian skin to monochromatic (single wavelength) irradiation varies markedly with the wave-

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length of the radiation. The production of erythema and the subsequent production of melanin pigment are both maximum with 296.7 mμ radiation (1, 2). As the wavelength of irradiation increases, both responses fall rapidly, so that 10 microwatts/cm.^{2} of 307 mμ radiation, 100 microwatts/cm.^{2} at 314 mμ, 1000 at 330 mμ and 10,000 at 340 mμ are each equivalent to the effect of 1 microwatt/cm.^{2} of 296.7 mμ radiation in the production of an erythema. The production of pigment follows a somewhat different equivalence relationship. The formation of new melanin pigment is excited by the erythema produced. Thus, up to about 320 mμ tanning and erythemal response curves are substantially parallel. Above 320 mμ another photochemical mechanism results in the reoxidation of bleached melanin pigment present in the surface layers of the skin. In this wavelength range the tanning response is the sum of the two mechanisms.

A unit of erythemal flux, the E-viton, is equivalent to the erythema induced by 10 microwatts/cm.^{2} of 296.7 mμ radiation. The response of the skin to an E-viton(or Viton) is constant: irradiation by 10 vitons for one hour produces the same erythemal response as does 5 vitons for two hours. On this basis also, the effects due to irradiation by different wavelengths are additive. The distribution of this erythemal flux in sunlight is shown in Fig. 1, averaged for 5 mμ bands. This curve corresponds to a total of 2.59 vitons. Since it takes about twenty minutes exposure to midsummer sunlight to produce a minimum perceptible erythema (MPE) on "normal" Caucasian skin, this corresponds to an exposure of about 3100 viton-seconds. Approximate response of "normal" Caucasian skin has been determined, and the values are shown in Fig. 2.

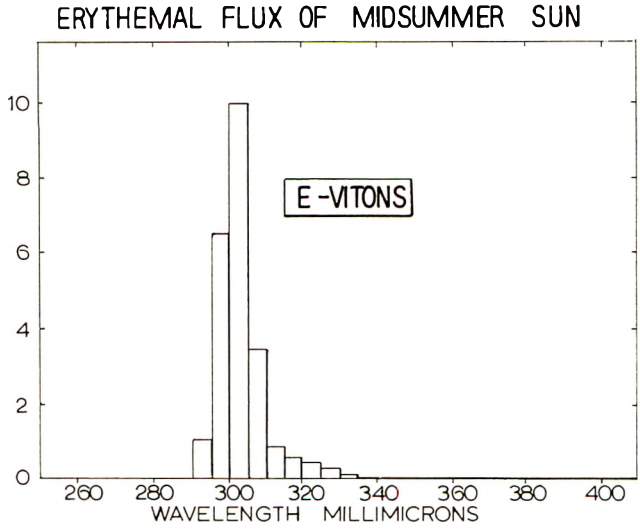


Figure 1.—Erythemal flux of midsummer sun.

Effect of Topically Applied Sun Screen on Incident Radiation

The function of the sun screen is to absorb the irradiating energy before it falls on the skin and produces an erythemal response. The nature of the protection desired will determine the amount of screen to be used in the preparation. For example, to protect an "average skin" during a four-hour, midday midsummer exposure from more than a vivid erythema, the viton-second exposure of the skin should be reduced to a maximum of about 6000 viton-seconds. The unscreened sunlight exposure during this period will amount to about 37,300 viton-seconds. Simple arithmetic shows that the screen should transmit no more than 16.1% of the incident viton units to achieve this result. A preparation which transmits as much as 32% of the viton units will produce a painfully sunburned subject, while

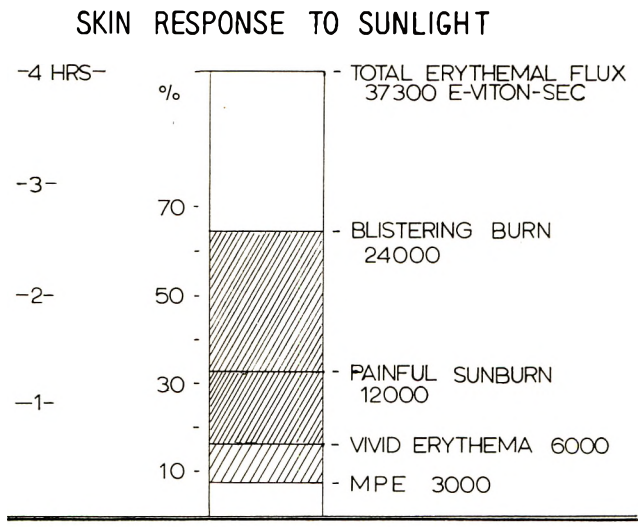


Figure 2.—Skin response to sunlight.

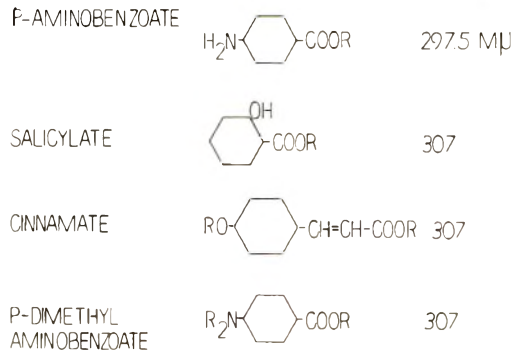
an 8% transmission will result in less than an MPE. These are, of course, average figures, with no real meaning for the individual case. But an examination of the practical level of transmission in marketed suntan preparations indicates the validity of this correlation of viton transmission with actual use.

For example, 2% of glyceryl *p*-aminobenzoate in a lotion base has been successfully used for many years for a widely applicable single-strength suntan. This transmits 7.5% of the incident viton units. A screen containing 6% of a salicylate has been widely marketed as a minimum-protection suntan. This rapid-tanning product transmits 15% of the incident viton units. Preparations which transmit more than 15% have

not found continued market acceptance, and such products usually do not reappear on the pharmacists' shelves after a short time. While this is a completely pragmatic correlation, it is an excellent one, because of the size and random character of the sample involved: the entire sun screen-using public. A third example of a successful preparation is one for so-called sun-sensitive users. Using 4% propylene glycol mono-*p*-aminobenzoate, it transmits 0.95% of the total incident viton units. The screen itself is not a total block at 2% concentrations, but increase in the concentration of the screen to 4% produced the effect desired in a total block.

Special Requirements of Sun Screens

The spectrophotometric qualities of a sun-screening chemical are only a part of the requirements these materials must meet. Structurally, the sun screen candidate compound must be able to resonate between alternate ionic forms (3). This ionization change must require an energy quantum within the ultraviolet region. This corresponds to electronic transition (ionization) energies of 91.4 to 99.4 kcal./gm. mol for compounds with absorption maxima between 290 and 315 mμ, the so-called erythemal range (Fig. 3). Few classes of compounds satisfy this basic requirement. All of the effective sun screens for human use are found in a very few types of aromatic compounds: *p*-aminobenzoates, *p*-dialkyl aminobenzoates, salicylates and cinnamates. Chemical structures and wavelengths of maximum absorption for these classes of screens are shown below:



Once the proper spectral absorption has been achieved, many other factors require attention. These include spectral stability, resistance to chemical and photochemical change, minimum percutaneous absorption, sufficient solubility in permissible vehicles but relative insolubility in water, compatibility with the usual ingredients of skin lotion formulations and freedom from any toxic or sensitizing skin reactions. Some of these requirements are obvious enough to require no further comment here, but the import of one of these factors is not generally realized.

Minimum percutaneous absorption is a very important factor. A sun screen film is effective only as long as the screen remains interposed between the surface of the skin and the sunlight. If it is absorbed through the skin it no longer can exert the necessary screening action. This is easily demonstrated in practice. For example, a lotion containing about 8% homomenthyl salicylate transmits 7.5% of the incident viton units, sufficient to prevent an MPE. If a skin patch is immediately exposed for 14 minutes under a standardized ultraviolet lamp after application of this lotion, an MPE is produced (14 minutes on the standard lamp is equivalent to four hours of midday midsummer sunlight). If an immediately adjacent patch is exposed to the lamp for 3.5 minutes each hour over a four-hour

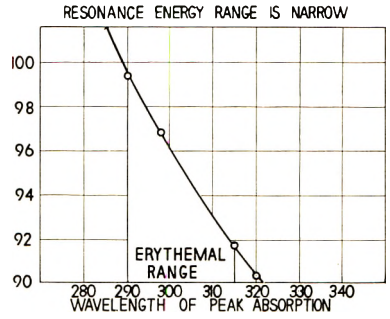


Figure 3.—Molecular resonance energy (kcal./gm. mole) determines wavelength of peak absorption.

period, the same total irradiation is achieved. But the result is an extremely painful sunburn. Care was taken during the test to keep the test patch untouched and immobilized, so that the only losses of screen which could possibly occur would be through percutaneous absorption. Such absorption of the screen reduced the effective surface concentration to the point where much more than the expected viton dosage was transmitted to the skin. A similar test with glyceryl-*p*-aminobenzoate at a concentration of 2% in the same lotion base, which also permits nominally 7% viton transmission, resulted, in the delayed test, in a vivid erythema without any sensitivity. This screen was the more effective of the two because it did not disappear by absorption into the skin as rapidly as did the salicylate.

Conclusion

Quantitation of skin response to irradiation by sunlight makes it possible to design a suntan preparation for any desirable degree of protection. Factors other than screen concentration in the suntan must be considered. Especially important is the rate of percutaneous absorption of the sun screening compound. When this is marked, the concentration of sun

screen required to afford a desired level of protection would be greater than that indicated by *in vitro* spectrophotometric measurements.

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THE STRUCTURE, FUNCTION AND FORMULATION OF TOPICAL SUN SCREENS II. PRACTICAL PROBLEMS

By HERMAN E. JASS, PH.D.*

Presented May 8, 1963, Semi-Annual Scientific Meeting of the Society of Cosmetic Chemists Held in Joint Sponsorship with the American Medical Association Committee on Cosmetics

ABSTRACT

Factors which govern the use of topical sun-protective products are skin type, average exposure, general usage and climatic conditions.

Virtues of sun-screening agents from the standpoint of the cosmetic and pharmaceutical formulator are described. These include absorption spectrum, absorptivity, solubility, stability and pharmacological inertness. Some factors involved in proper formulation of sun screens and their vehicles are explained. Finally, the evaluation of the finished product from the standpoint of safety and effectiveness is described.

I. INTRODUCTION

The use of sun-protective products by people desiring to eliminate painful burns suffered by exposure to the sun has grown considerably over the past 30 years. Fortunately, the scientific formulation of these products has been continuously improved. However, there has been a recent tendency observed in technical and lay publications to deprecate the effectiveness of commercial sun-protective products. These criticisms assume that only a broad-spectrum ultraviolet screen in high concentration is worth considering. This view stems in part from the work on irradiation-induced carcinomas in mice by Blum (1–3) which led to his theory on the quantitative, irreversible relationship between ultraviolet dose size and the term of growth and incidence of skin cancers. In addition, the demonstration of aging effects on the exposed skin of fair-skinned individuals in areas of high UV incidence by Knox (4) reinforced this belief. Knox also evaluated a number of commercial sun preparations (5) to determine their minimal erythemal dose on albino rabbits and concluded that these preparations were only minimally effective.

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From a public health point of view, a total barrier, high-concentration screening product is warranted in selected situations. These include the fair-skinned person living in tropical or semitropical areas who spends much time outdoors or even the temperate climate dweller who is chronically exposed to the sun through occupation, such as a farmer or sailor. However, not all of us are fair-skinned, or continuously exposed outdoors, or live in high UV incident areas.

The Revlon Research Center has conducted *in vivo* tests on both normal and sensitive-skinned persons in midday Florida sun in the course of developmental testing of new products. The tests were performed by exposing the backs of previously unexposed persons to which various test products had been applied. Variable factors included skin type, exposure time, sun screen type, sun screen concentration and vehicle type. Immediately after exposure and one day and one week later the degree of radiation effects (reddening, blistering, peeling and tanning) was graded and evaluated, usually by analysis of variance. The results of these tests showed that products can be properly formulated to permit rapid tanning without residual significant erythema, blistering or pain after four to six hours exposure with single applications (6). They also showed that very fair-skinned subjects require significantly higher concentrations of sun screen to achieve the same period of protection as individuals with more heavily pigmented skin. However, where the ability to tan exists, both types of people desire a product that protects from erythema while allowing tanning to take place. In fact, tanning is beneficial in that it affords additional protection. Furthermore, evidence is strong that these tanning rays, that is, radiation above 320 mμ, do not produce epidermal damage (2, 7–10). It appears rational, therefore, for the market place to exhibit more than one type of sun-protective product. The important qualifications should be thorough testing, as described below, to determine safety and effectiveness and clear, proper directions for use which reflect its intended applications.

II. Development of Practical Sun Screen Products

A. *Concentration of Sun Screen*

A primary consideration in formulating suntan products is the concentration of the sun screen compound. Figure 1 presents the ultraviolet absorption spectra of three typical erythemal range screens: dipropylene glycol salicylate, glyceryl *p*-aminobenzoate and isobutyl salicylcinnamate at concentrations adjusted for normal tanning. Note that despite the disparity in their concentrations and in the wavelength of their maximum absorption they exhibit approximately the same cutoff value, 95–98% transmission at 320 mμ. However, to achieve this high level of transmission at 320 mμ, the absorption in the erythemal range of the salicylate has

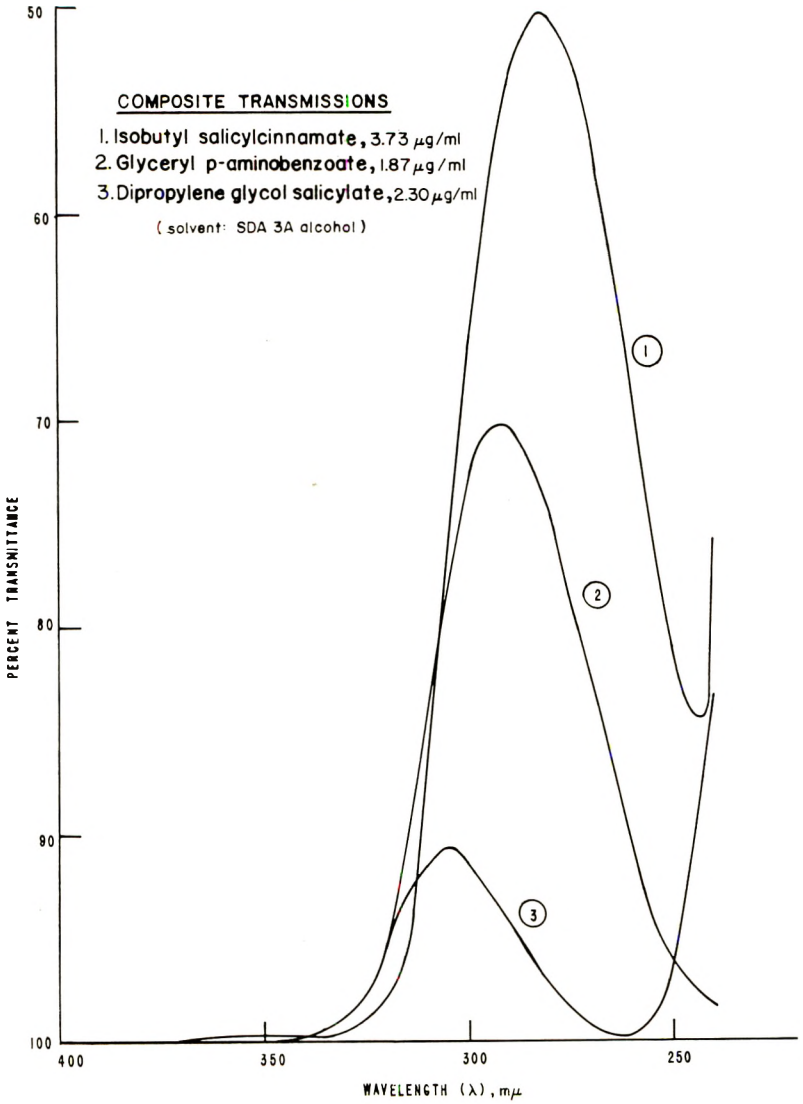

Figure 1.—Ultraviolet absorption spectra of three typical erythemal-range sun screens.

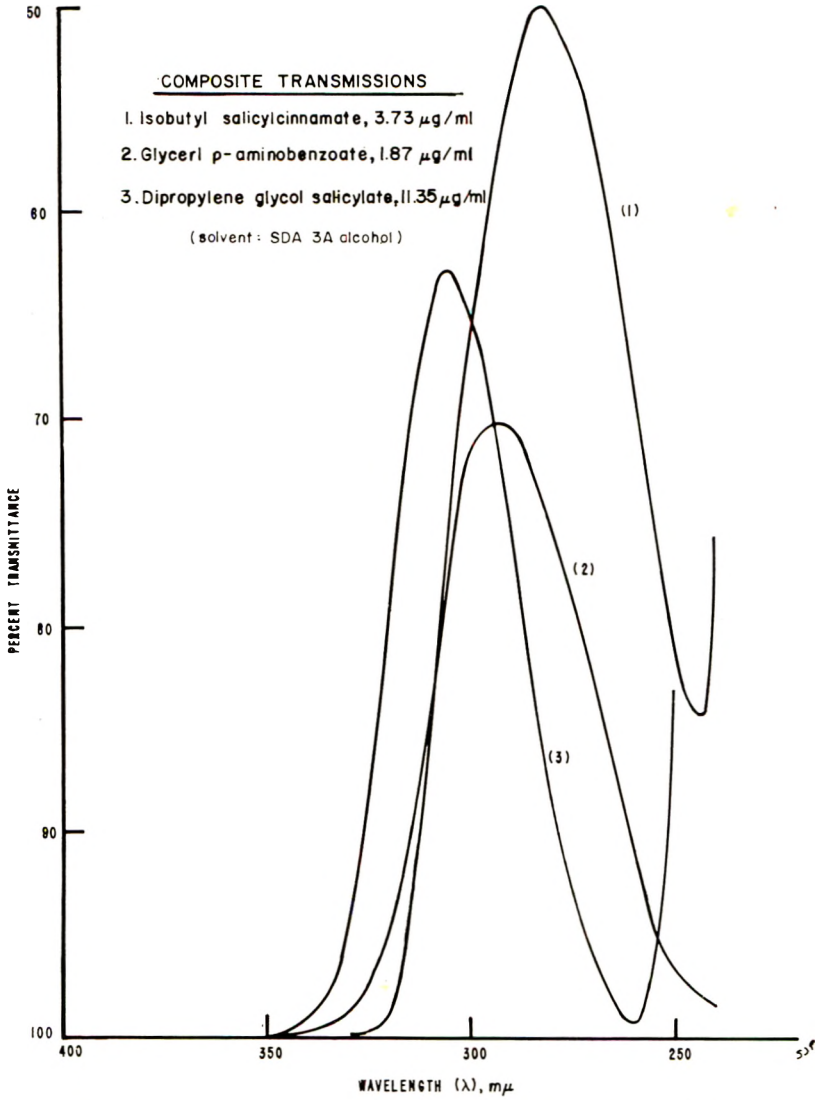

Figure 1a.—Sun screen spectra shown in Fig. 1; adjusted concentrations.

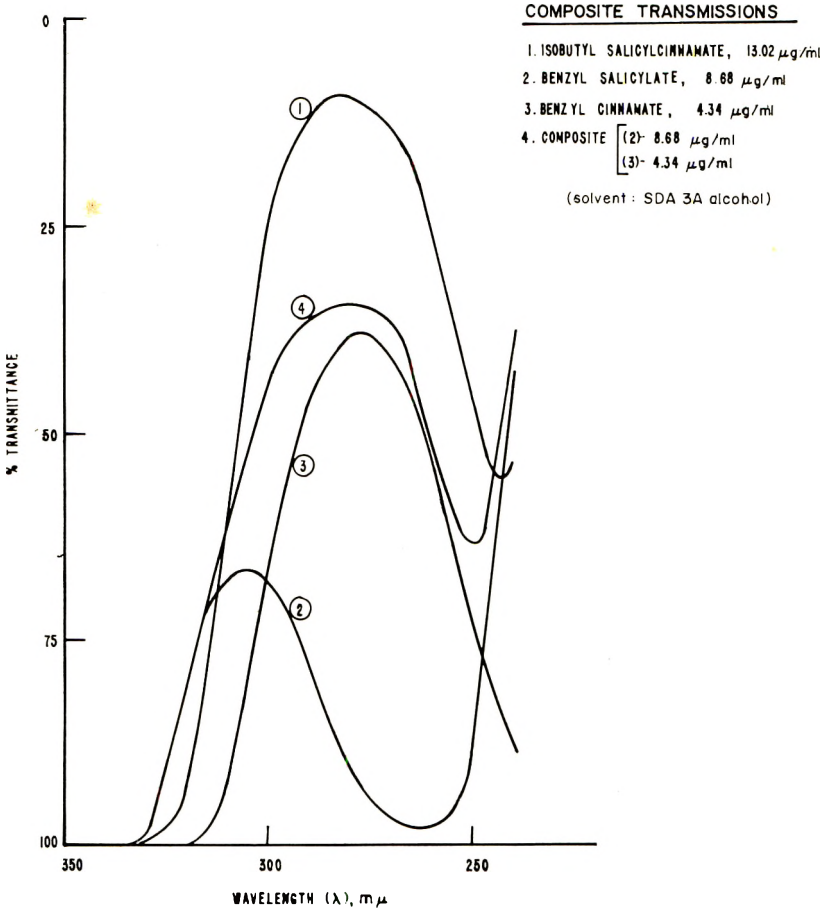

Figure 2.—Ultraviolet absorption spectra of salicylates and cinnamates.

been reduced to much too low a level. When the concentration is increased to afford proper erythemal protection, a considerable fraction of the tanning range (i.e., above 320 mμ) will be screened out also, as shown in Fig. 1a. One solution would be to combine this screen with another whose ultraviolet absorption range is lower in the spectrum. One of the first commercial suntan products utilized a blend of benzyl cinnamate and benzyl salicylate. Figure 2 shows the desirable effect of combining these two screens to achieve a proper range of absorption. Incidentally, although undesirable side effects have been reported for the above mixture, the synthesis of the cinnamate and salicylate moieties into one large, bulky and physiologically inert molecule, an alkyl salicylcinnamate (cf. curve 1, Fig. 2), preserves the advantageous absorption characteristics and eliminates the side effects.

This may be due to a reduction in percutaneous absorption due to its larger molecular size. In any case, however, the use of sun screen combinations to achieve desired screening effects is feasible but insufficiently utilized.

B. *Film Thickness*

Film thickness on the skin is an important factor in evaluation of product effectiveness. Concomitantly, variability of the viscosity of the product at high ambient temperatures, which affects spreadability and film thickness, should be considered. Figure 3 indicates the difference in results obtained from two lotions where the only difference was that one product had a flatter temperature-viscosity curve. It also follows and should be emphasized that indoor laboratory testing with UV lamps may erroneously indicate high protectiveness for a product, due to lower temperatures encountered under these conditions. Clear fluid vehicles and aerosol sprays normally require markedly higher screen concentrations due to the thinner film laid down on the skin.

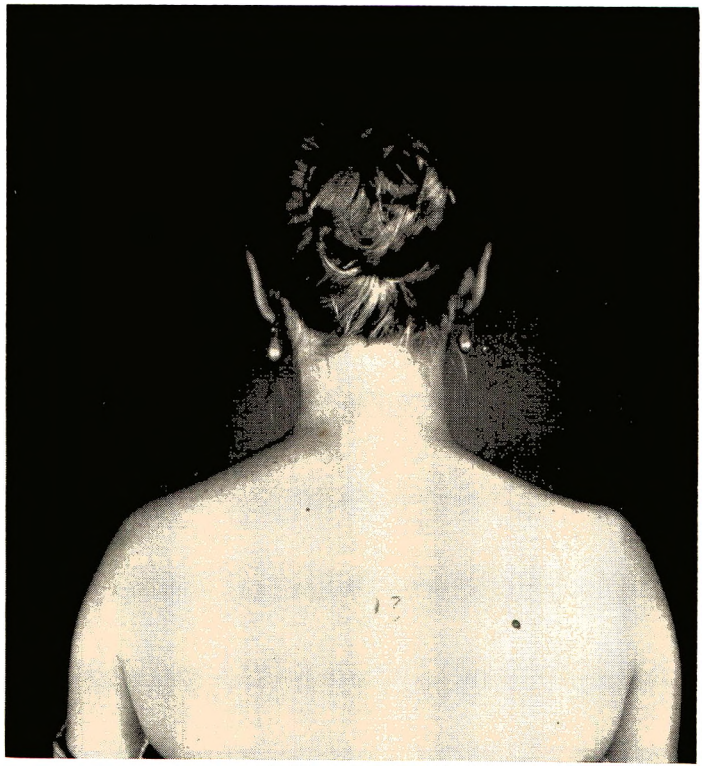

Figure 3.—Effect of viscosity of sun screen vehicle on protectiveness. Product applied on left has half the viscosity (Brookfield) at 100°F. as product applied to right. Viscosities at 70°F. are equal.

C. *Stability of Screening Agent*

Another factor to be taken into consideration involves the stability of the screen to irradiation. It may be converted to a nonabsorbing film, which requires periodic reapplication, or to a discolored or otherwise deleteriously altered form. Screens should be carefully evaluated for their safety to clothing to ensure freedom from staining. Stability of the applied product film to washing and sweating should be ascertained. Sun screens, being organic molecules, usually esters, are generally water insoluble. However, the vehicle may be water soluble or dispersible, which can cause re-emulsification of the sun screen. The degree of resistance to washing may be tested in the laboratory by bilateral applications of the product to the backs of several subjects followed by the rinsing of one side with measured quantities of water, followed by the irradiation of both sides to the point of minimal erythema. If significant differences in erythema are seen, the product label requires clear warning to reapply after bathing, although possibly reformulation should be considered. Reformulation may include addition of a component to inhibit re-emulsification or selection of a different emulsifier system, for example, an anionic system instead of a nonionic type.

Percutaneous absorption of the sun screen is a factor which can rapidly reduce the protectiveness of a composition. In addition, a high rate of absorption can enhance any tendency toward physiological sensitization that may be inherent in certain molecular configurations. This aspect of sun screen stability is discussed more fully in Part I of this paper (11).

III. Testing of Practical Sun Screen Products

A. *Laboratory Testing*

Testing for effectiveness starts with UV spectrophotometric evaluation to determine the absorption range and capacity. These may be expressed as E-vitons (12), Sun Screen Index (13), or K-value (14), any of which may be utilized, provided that comparisons are made to the values for a known standard.

The second stage of testing is normally done on humans and utilizes a mercury-vapor lamp. The use of the vapor lamp suffers from two disadvantages: (1) the temperature differences mentioned previously and (2) the differences in ultraviolet emission between the mercury spectrum and actual sunlight. For this reason certain precautions must be taken. The experiment must be well-controlled in terms of amounts applied, method of application, and similarity of vehicle, and also in terms of experimental design.

A Latin-square design (15), including sufficient replications, is one example of experimental design which yields results with good precision.

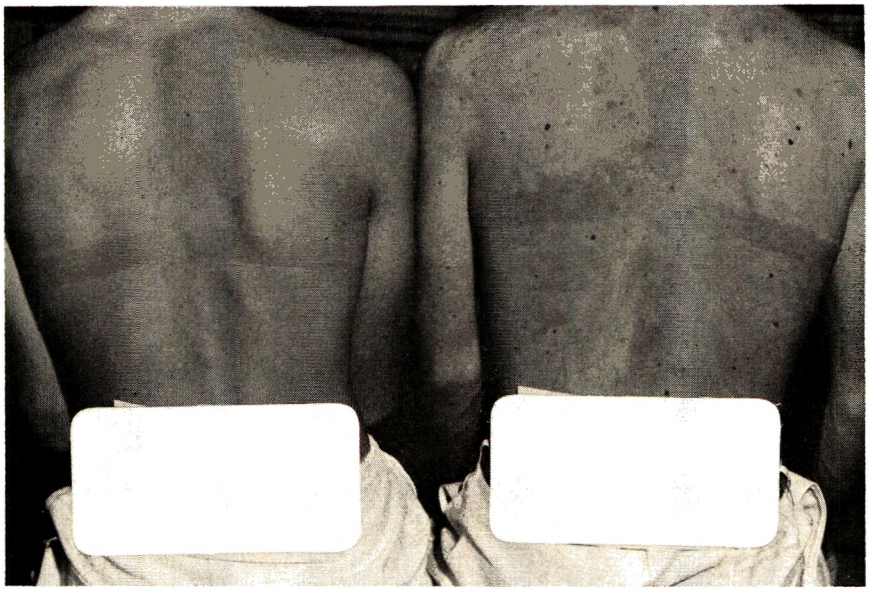

Figure 4.—Two subjects on a four-treatment Latin-square sun screen evaluation test in the process of being scored. The vivid erythemal bands are unprotected areas.

Included in the evaluation should be a standard control, the material to be evaluated, and two similar compositions with screen concentrations in one case lower and in the other higher than the test product so as to evaluate properly the optimal screen concentration. A strip of unprotected skin is exposed in order to act as an indicator of erythemal dosage. The day after irradiation a panel of judges independently scores the degree of residual erythema, using a numerical rating provided beforehand. The results are totaled, and the optimal formulation picked as either equal to or better than the standard control, or allowing no erythema, depending on the chosen goal. Rank tests may be used if necessary and applicable. Figure 4 shows two subjects being scored.

Adequately supervised clinical tests performed under actual sunlight are the critical phase of the testing program. Here again, a standard control product should be used, a small area left unprotected as a blank control, and a recording UV light meter used to record total radiation. The test and control products are applied equally to left and right sides of the back. The results are evaluated as described above.

B. *Use and Safety Testing*

Finally, actual use-testing on large consumer panels is highly desirable to determine over-all effectiveness, freedom from side-effects, acceptability of formulation and general consumer acceptance. These use tests are

necessarily short in duration since suntan products are generally utilized on week ends and vacations. Because of this, the accumulation of sufficient data may be drawn out over a long period of time due to the sporadic use pattern.

Tests for safety have been greatly standardized for topical products and need not be described in detail here. There are special tests which apply to sun-protective products specifically which are worth mentioning. Since suntan oils and creams are often utilized to soothe sunburned skin in contrast to their intended use, it is well to patch test them on skin purposely injured by irradiation. Also, since adventitious contact with the eye is quite probable for a number of obvious reasons, actual voluntary applications to the eye, after satisfactory results have been obtained on a Draize-type eye irritation study (16), is a recommended procedure. Finally, it is an advisable procedure to expose test subjects, with product properly applied, to irradiation past the minimal erythemal dose in order to uncover possible irritants resulting from the actinic decomposition of the product and in order to observe the effects of these irritants on damaged skin. Needless to say, this test should be applied to laboratory animals first.

IV. Conclusions

To summarize, sun-protective products with different degrees of protectiveness are both necessary and desirable for the consumer market. The tendency to deprecation of tanning products which screen out erythemal radiation only is not justified when these products are adequately formulated. However, because effectiveness and safety in use are so intimately connected in the area of sun-protective products, evaluation of both of these factors is equally important. Testing should be systematic, well-controlled and accurate. The results should be properly evaluated, generally by using statistical methods.

Since laboratory conditions may not be easily arranged to duplicate use conditions, (e.g., mercury vapor lamp and natural sunlight) actual field testing must be utilized finally to determine the product's utility as a sun-protective composition. Label copy should indicate clearly the skin type for which the product is intended, the directions for use, duration of protection and contraindication. In this connection, it should be mentioned that even minor changes in vehicle composition call for re-evaluation of effectiveness due to the effects these changes may have on film thickness, water dispersibility and other factors.

It is probable that formulation of sun-protective products will continue to become more specific, with products designed not only to satisfy different skin type needs but other considerations as well. These might include products for short-term or prolonged or continuous exposure, complete protection for the unfortunate individual suffering from serious local or

systemic disease aggravated by sunlight, and customary cosmetics with ultraviolet screening as a secondary property. In any case, the use of sun-protective products should become as universal as shaving for men or the use of lipstick by women. For this growth to occur, to the benefit of the consumer and manufacturer alike, the formulation and testing of sun-protective items must continue to become more scientific and critical in the future.

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THE ANATOMY OF SWEAT GLANDS*

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Abstract

The morphology and distribution of the two different types of sweat glands in the skin of man are described. Differences between eccrine and apocrine sweat glands are discussed in terms of their function, anatomy, histochemistry and secretion.

Introduction

Man sweats readily and profusely. Sweating is, in fact, one of man's most characteristic biological attributes.

Even those who receive much of their education from television commercials know that we have two types of sweating apparatuses. The two types of sweat glands, *eccrine* and *apocrine*, were clearly recognized and named only in 1922 by Schiefferdecker, who pointed out that most other mammals have apocrine sweat glands over their body and have eccrine sweat glands restricted to specialized areas. In the members of the order Primates, to which man, the "monkeys" and the apes belong, apocrine glands gradually disappear from the skin of successively higher forms at the same time that eccrine sweat glands take their place. The replacement is almost complete in man, in whom apocrine sweat glands are largely rudimentary or absent over the larger surface of the body. Apocrine glands abound only in the external auditory meatus, the axilla, the periumbilical area, the anogenital skin and the nipples of the female breast (Fig. 1). A few may be found almost anywhere on the body. Since most other mammals have only apocrine sweat glands over the body surface, and the more advanced Primates have both apocrine and eccrine glands, it is appealing to think that apocrine glands are most ancient phylogenetically and more primitive than the eccrine sweat glands. If this is correct, the apocrine sweat glands of man are relics of a primitive organ system. Lest

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one be swept away by this attractive idea, let him reflect that the duck-billed platypus, the most primitive living mammal, and the tree shrew, the most primitive Primate, both have highly differentiated eccrine and apocrine sweat glands. One cannot assume, therefore, that the organs of extant animals can give us enough information on the phylogenetic history of these organs to allow us to reconstruct their evolutionary path. Similar organs can develop independently in different orders of mammals.

The Eccrine Sweat Glands

Although present in limited numbers in the skin of other mammals and in great numbers in some of the more advanced nonhuman Primates, no other animal has as many eccrine sweat glands over the entire body surface as has man, and in no other animal are the glands as highly functional. Man has two to three million eccrine sweat glands over his body surfaces. There are more in some regions than in others, and some individuals have more glands than others. On the face, for example, there are twice as many as on the leg, and on the trunk there is an intermediate number (1). Both sexes have about the same number of glands. In a survey of the skin of the fetus, the child and adult, one finds a gradual reduction in the number of glands per unit area of skin as the individual attains full size and maturity. This reduction is brought about by the expanding body surface which spaces the glands farther apart, their total number remaining the same.

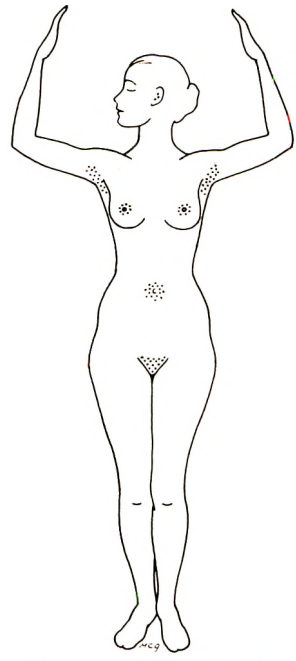

Figure 1.—Diagram showing the major sites of concentration of apocrine sweat glands on the human body.

The glands appear first in fetuses, three to three and a half months old, only on the volar surfaces of the hands and feet (Fig. 2). None develop elsewhere at this time. The recognizable anatomical details of these glands develop slowly, extending over a period of several weeks. Glands do not differentiate on the hairy surfaces until five to five and a half months, usually grouped in characteristic patterns around hair follicles. When these begin to develop, the hair follicles and their sebaceous glands are already completely differentiated and functional. In the scalp, the follicles have already gone through one complete cycle of growth at the time that sweat glands appear. The glands develop dyschronously; they are seen first in the axilla before they appear anywhere

Figure 2.—Eccrine sweat glands developing on the volar surface of a finger in an embryo $3^1/_2$ months old. Treated to demonstrate phosphorylase activity.

else. Thus, in the same fetus, glands can be histologically differentiated in one area and undeveloped in another.

It would seem permissible here to speculate upon the possible meaning of this dyschrony of events in terms of function. Since the glands on the friction surfaces and some of those in the axilla develop before those on the hairy surfaces, and these respond primarily to psychogenic stimulations, whereas those on the hairy surface respond to thermal stimulations, perhaps eccrine sweat glands should be divided into two groups. This is in agreement with Kuno (2). The glands in the palms and soles and those of the axilla may be the more ancient, and those in the hairy skin may be more recent organs. If this should be correct, the response to psychogenic stimuli would be the original function of eccrine sweat glands, mostly to maintain the friction surfaces moist, thus enhancing tactile sensibility and grip. The glands elsewhere on the body, having arrived later, could be just learning the new function of responding to thermal stimulation.

The two types of glands are also different anatomically. The diameter of the duct of the glands on the palms, soles and axilla is less than one-half of the diameter of the secretory segment. In contrast, the diameter of the ducts of the glands in the hairy skin is roughly the same as that of the secretory coil. All other details are similar.

The general anatomy, histology and histochemistry of sweat glands are well known; only some of them will be discussed briefly. A detailed account of these is found in a recent monograph (3).

Eccrine sweat glands are simple tubes that extend from the epidermis to midway in the dermis or deeper. Each gland has an irregularly coiled basal segment, a straight segment that extends from the coil to the epi-

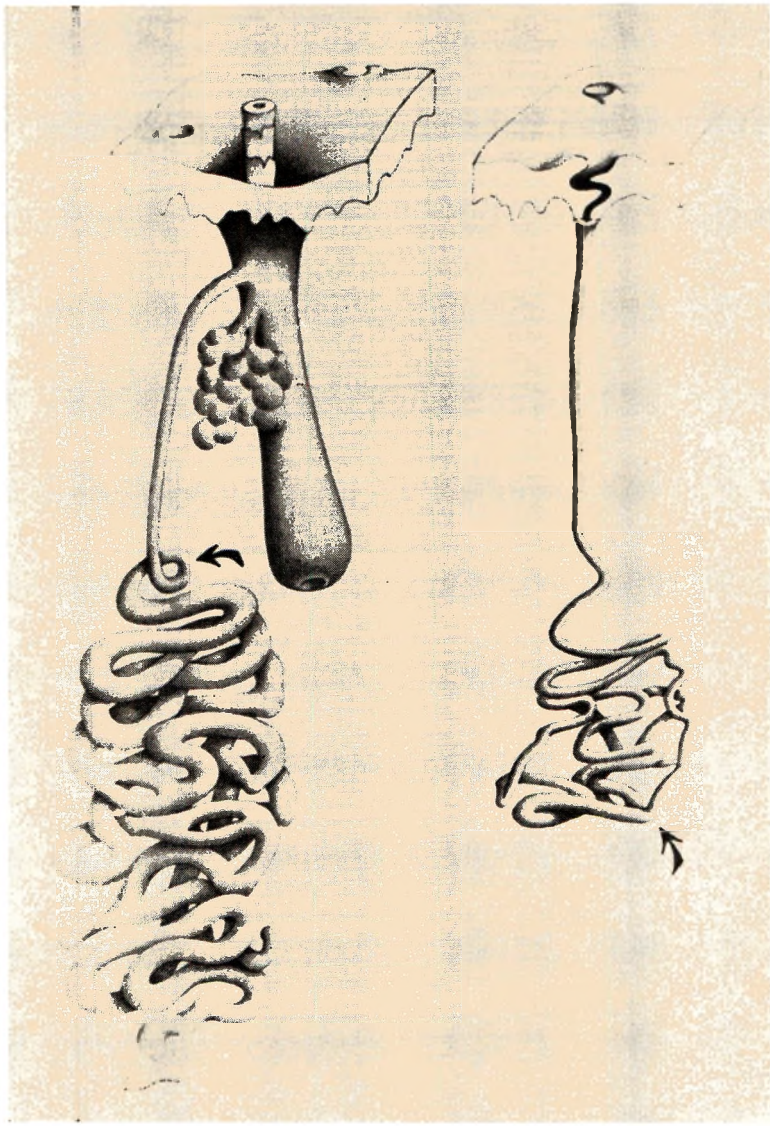

Figure 3.—Diagrams showing an eccrine sweat gland on the right, and an apocrine sweat gland with the duct emptying into a pilary canal on the left. The arrow indicates the transition from secretory segment to duct.

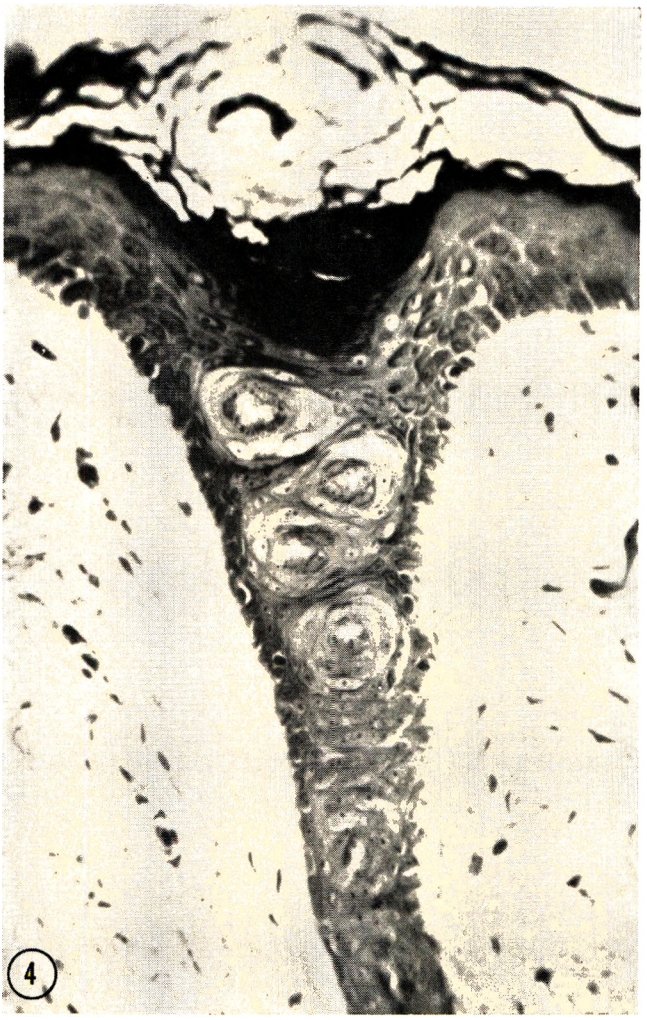

Figure 4.—Section through an intact, so-called "epidermal sweat duct unit" from the axilla. The duct outlines a cone; the lumen, which has been cut several times, becomes progressively larger as it approaches the surface of the skin.

dermis, and a terminal spiral segment that is encased within the epidermis, "the epidermal sweat duct unit." About one-third of the basal coil consists of duct and two-thirds of it secretory segment (Fig. 3). The duct, then, comprises the greater part of the total gland (Fig. 4).

The secretory epithelium consists of two types of cells: smaller ones crowded toward the luminal border which stain with basic dyes, the "dark cells," and larger ones toward the base of the tubule which stain poorly with basic dyes, the "clear cells" (Fig. 5). The cytoplasm of the dark

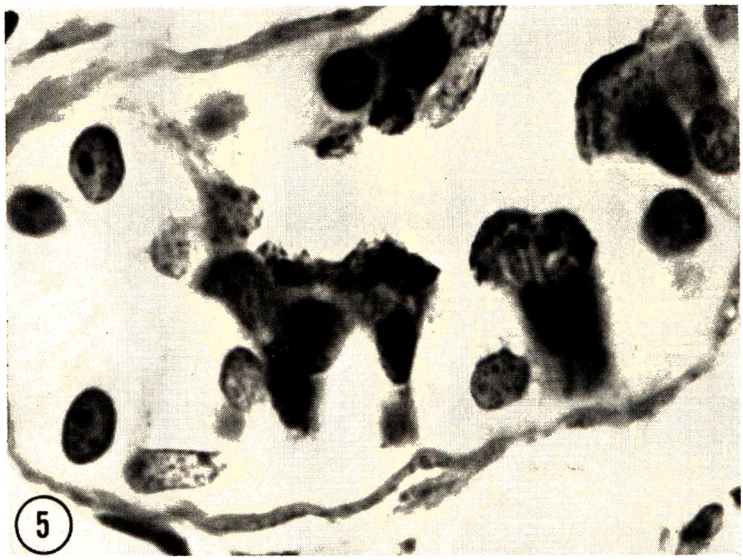

Figure 5.—Section through an eccrine sweat gland, stained with toluidine blue to show the "clear" and "dark" cells.

cells abounds in ribonucleic acid and mucopolysaccharides, both of which stain avidly with basic dyes; that of the clear cells contains small amounts of these substances. Clear and dark cells, but mostly the clear cells, contain variable amounts of glycogen. When the glands are overworked, the glycogen usually, but not always, disappears (4). Between the secretory cells and the basement membrane is a layer of myoepithelial cells, which fit together loosely like the staves of a barrel. These cells, though believed to contract to aid the expulsion of sweat, are really a cellular skeleton that gives support to the friable tubule and prevents it from collapsing.

Eccrine sweat glands are lively biological entities. A large list of enzymes have been localized in them, in the ducts as well as in the secretory portion. Among these are cytochrome oxidase, succinic dehydrogenase, MAO, beta glucuronidase, amino peptidases, amylophosphorylases and others (3). Alkaline phosphatase is precisely localized in delicate canaliculi between the clear cells. Studies with the electron microscope confirm the presence of these canaliculi; their structure suggests that they are secretory surfaces. Sweat from the clear cells, therefore, passes into the lumen by way of these canaliculi.

The secretory segment is encircled by many nonmyelinated nerves which contain cholinesterase (Fig. 7). The predictable presence of these nerves is one of the distinctive features of the eccrine sweat glands. The entire gland is abundantly supplied with blood vessels. This vascular network, precise in the skin of children, becomes less so in that of the adult, in which the vessels anastomose with the other vessels nearby.

The anatomical features of the duct are so different from those of the secretory coil that the transition from one to the other is abrupt. The duct consists of two or three layers of cuboidal cells. The luminal cells have a variably keratinized hyalin, or cuticular border, which gives the structure enough rigidity to prevent it from collapsing when the skin is compressed (Fig. 6) (5). The terminal segment of the duct, inside the epidermis, follows a helical path. The majority of these helices have a right-handed coiling which Takagi (6) regards as normal (Fig. 4). The coils of the spiral become progressively larger as they ascend to the surface of the skin, outlining a conical pattern; the lumen also becomes increasingly wider as it nears the orifice. Structurally well delineated upon the fric-

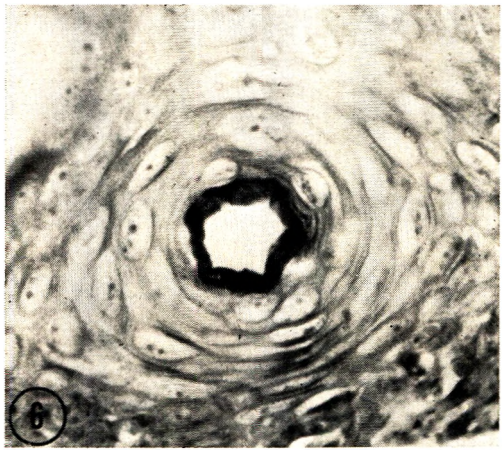

Figure 6.—Transverse section through that portion of the duct where it joins the epidermis: the clearly differentiated cuticular border has great concentrations of disulfide groups.

tion surfaces, the orifices of the glands in the hairy skin are less clear. On the hairy skin, the glands open to the surface at such a steep angle that the stratum corneum of the epidermis acts as a sort of operculum which often masks the slit-like pore.

There has been much unnecessary controversy about the possible role of the duct in sweating. Omitting all details, which those interested may find elsewhere (3), it is moderately certain that the duct is more than a passive conduit for sweat, and perhaps it functions in the selective reabsorption of water and other substances from the sweat.

The Apocrine Sweat Glands

For fuller information on the structure, physiology and pharmacology of apocrine sweat glands, the reader is referred to Hurley and Shelley (7), Montagna (8) and Aoki (9).

The diversity in structure of these glands, even in the same field, is so great that a generalized description defies accuracy. Differences occur at gross and microscopic levels. In the axilla, the glands display great diversity in shape, size and numbers. The focal point of glandular development is the center of the axillary vault, where nearly every hair is associated with one very large gland. The glands become progressively smaller and sparser toward the periphery of the axillary organ. In the vault of the axilla, variably dilated glands form a solid mass (Fig. 8), crowded into the lower dermis and hypodermal fat. The nests of adjacent secretory tubules of each glandular unit, though well defined elsewhere, are so jammed together here that they often encroach upon each other's

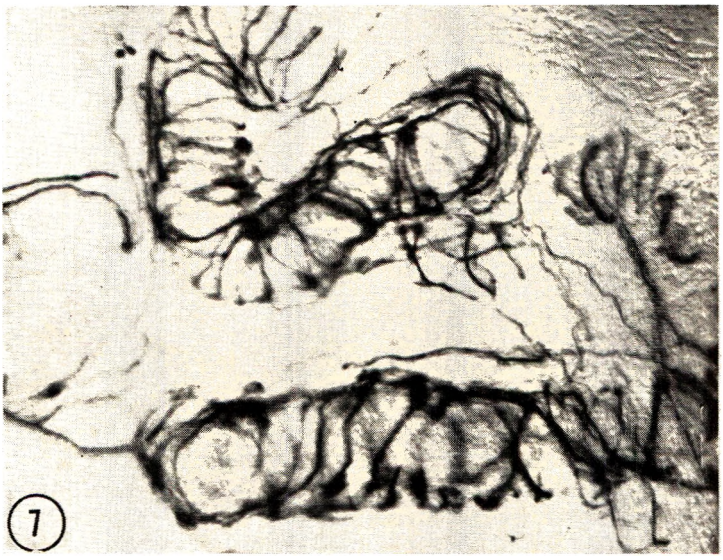

Figure 7.—Coils of an eccrine sweat gland surrounded by nerves.

territory (Fig. 4). Great diversity occurs in the over-all size of the tubules (Fig. 10). Adjacent tubules of individual units fuse together, forming sponge-like mazes of interconnecting channels. A single, uninterrupted canal, such as that found in the eccrine sweat glands, is no longer present. Any one nest of tubules, representing a single gland, may have portions blocked off, which may be cystic and dilated, while other portions may be structurally unaffected. Differences occur in the outer diameter of the tubules and the glandular tissue often appears cavernous. Some segments, blown up like balloons, are thin walled, whereas adjacent ones may be only a fraction of their diameter and thick walled (Fig. 10). An emphasis upon the varieties of size and form, however, should not allow one to forget that many glandular units are uniformly of one type or another.

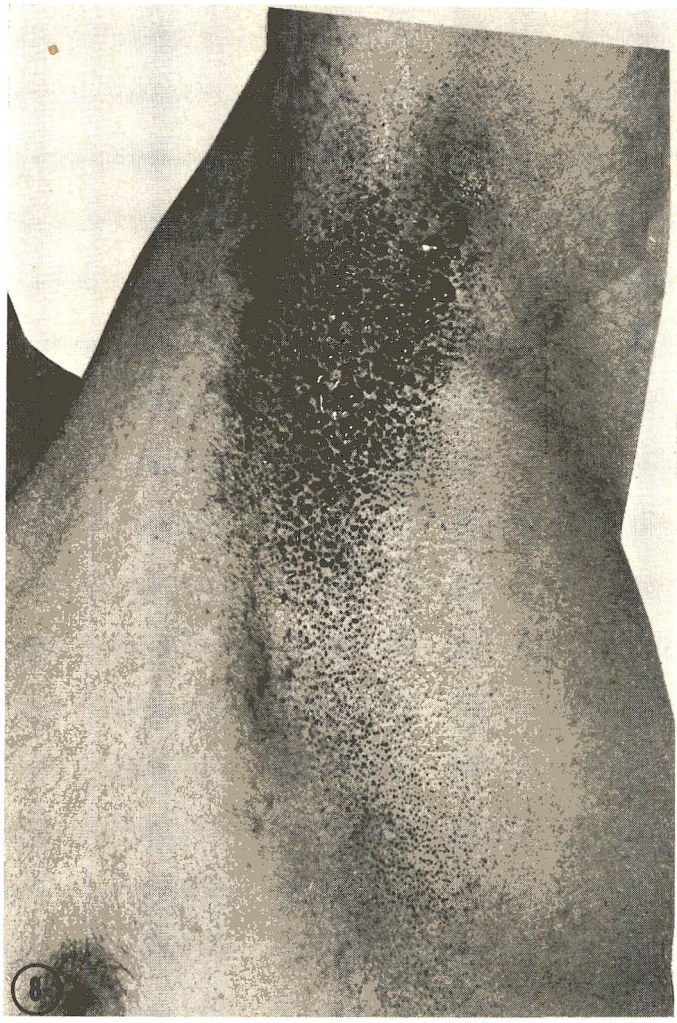

Figure 8.—Beads of eccrine sweat on the axilla of a young man exposed to a hot environment. (Courtesy of the Colgate-Palmolive Co.)

It is difficult to give a description of the cytological details of an organ which is characterized by such vagaries in structure. All of the secretory cells, however, are of one sort. Yet, the structural expression of this one type of cells is limitless. In the axilla of young adults, the majority of the tubules are lined with columnar or cuboidal cells. Most cells, regardless of size, contain numerous pigmented granules in their cytoplasm, but some do not. Some tubules, whether dilated or not, are lined with very flat squamous cells. The lumen of some such tubules is full of still-intact, cast-off epithelial cells.

It is meaningless to emphasize that the glands secrete strictly by an apocrine or merocrine process. It seems to me that these glands are either confused or highly versatile; even though they secrete primarily by a merocrine process, like the eccrine glands, they can also function as holocrine glands.

The pooled secretion inside the various tubules in any one specimen has different histological properties. It may be clear, cloudy, flocculent, and it may contain casts of whole cells particulate. The secretion may be acidophilic, basophilic or chromophobic. It may stain metachromatically or orthochromatically with thiazine dyes, it may be PAS-positive, and it may even contain some glycogen, or it may have none of these properties. Such an array of discrepancies suggests that the chemical properties of the secretion may also differ in different glands, or that the properties change as the secretion ages within the tubules.

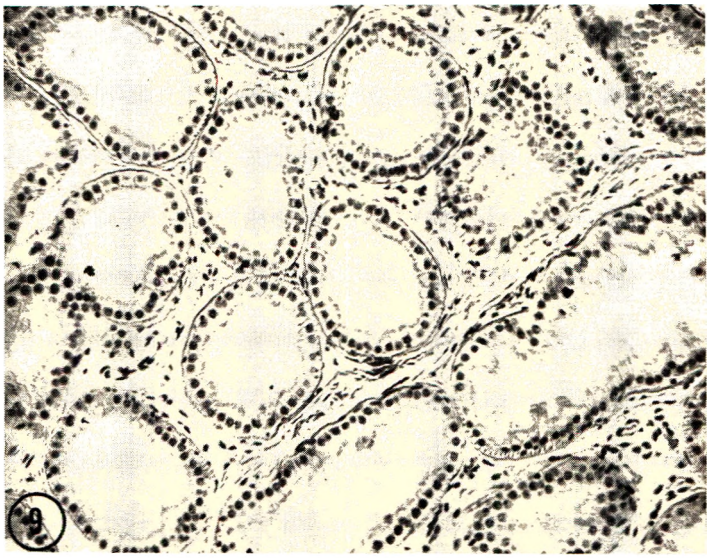

Figure 9.—Apocrine sweat glands from the axilla.

The glands develop in the five and a half month-old fetus, remain small through infancy and childhood, and gradually become functional in the late preadolescent years. They attain full development in young adults and begin to decline very gradually in middle age (10). The decline, more pronounced in women than in men, is not sudden, and structurally normal glands may be found even in old individuals. Since axillary odor is feeble or nonexistent in old people, either the glands have ceased to secrete, in spite of structural integrity, or the substance which they secrete does not produce a significant odor when it decomposes.

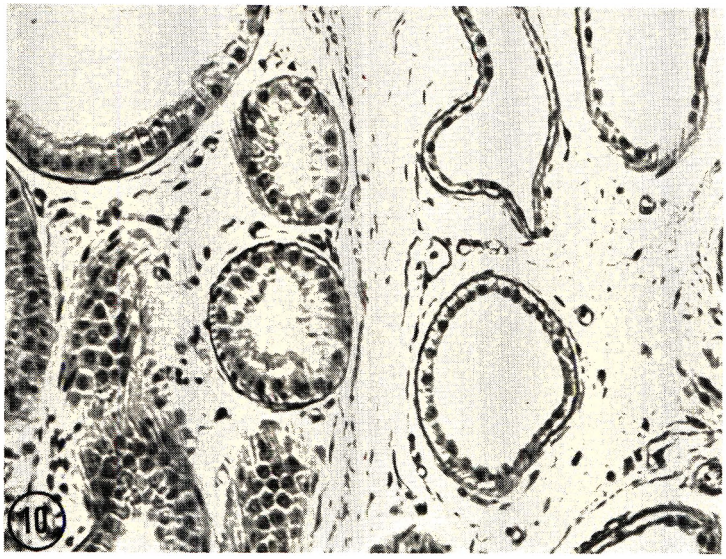

Figure 10.—Two apocrine sweat glands showing great differences in the height of the secretory epithelium.

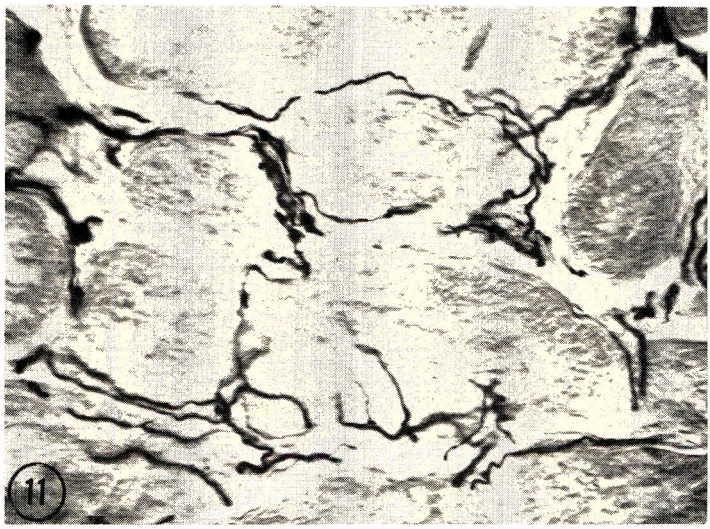

Figure 11.—Apocrine sweat glands (counterstained lightly by paracarmine) surrounded by a few coarse nerves which contain acetylcholinesterase. From the axilla of a Negro.

Too little attention has been given to the differences of apocrine glands in the two sexes and in different ethnic groups. Casual statements that the glands are better developed and more numerous in women than in men (11) and in Negroes than in Caucasians have little meaning until we have more information. Some significant differences have just been found; the glands of Negroes, for example, always have some nerves around them that contain cholinesterase (Fig. 11), but those of Caucasians rarely do (12). Other differences no doubt exist.

Summary

Eccrine and apocrine sweat glands are structurally very different and probably have different evolutionary history. At least in man, eccrine sweat glands serve only as thermoregulatory mechanisms, whereas apocrine glands are effectively scent glands, which must have served some social function when man was not so scrupulously fastidious as he is today. Although much has been made of the differences in physiological and pharmacological properties between the two types of glands, it is evident that each responds to both adrenergic and cholinergic stimulations. We now have impressive amounts of information on the structure of these glands, but we have just begun to correlate these data with the fragmentary and often discordant information gathered by the physiologists.

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BOOK REVIEWS

ELECTRON MICROSCOPY OF SKIN AND MUCOUS MEMBRANE, by Alvin S. Zelicson. Charles C Thomas, Springfield, Ill. 1963. 173 pages, illustrated and indexed. Price $8.50.

Intended as a primer for the active student in dermatology, this monograph covers a large area in a rather concise manner. Although probably too brief to be used according to the jacket claim ("a *text* for the clinical dermatologist"), the cosmetic chemist will find it a very useful summary of current knowledge of the ultrastructure of the skin.

The references are up to date (1962) and quite sufficient for the author's purpose. The illustrative photomicrographs are numerous and well chosen but often not reproduced sharply. This is unfortunate, especially to those of us who have had the pleasure of seeing the originals when they were published by such master craftsmen as Isser Brody and Cecily Selby in *J. Invest. Dermatol.* and *J. Ultrastruct. Res.*

The opening chapter is a 15 page essay by J. Francis Hartman on the electron microscope itself and techniques of specimen preparation. Following this is a general chapter on ultrastructure features of the cell; references to this chapter are extensive and are themselves divided into groupings such as The Nuclear Membrane, Mitochondria, Golgi Complex, etc. Next are three chapters on the epidermis and the keratinization process, followed by one on melanocytes and the melanin granule, subjects of personal interest to Zelicson. The final portion of the book is concerned with cutaneous appendages (sweat and sebaceous glands, hair), connective tissue and blood cells.

The book is very well organized and lucidly written. The interested cosmetic chemist, even though having relatively little special knowledge of this field, will find the text easy to follow and well worth doing so. It makes an excellent desk reference for quick checking of relatively unfamiliar terms and concepts encountered in biochemical and dermatological journals.—ROBERT L. GOLDEMBERG—Shulton, Inc.

THE HAIR AND SCALP, by Agnes Savill and Clara Warren. Williams and Wilkins Co. Baltimore, Md. 1962. 326 pages, illustrated and indexed. Price $8.75.

This book is written by a dermatologist primarily for dermatologists; nevertheless, it touches on material with which chemists, physiologists and others specializing in the science of human hair should be familiar. "Hair and Scalp" by Saville has undergone numerous changes since its first edition. This latest, fifth, edition still contains essentially the material of the earlier editions; in addition, many sections have been up-dated with new information.

The major part of this book is concerned with all disease entities which may, from time to time, invade or affect the hair or the scalp. It is thus not only about healthy and normal hair but also concerned with diseases of the hirsute areas of the

head. Of particular interest to cosmetic chemists are, of course, the earlier chapters covering the structure, physiology, physics and care of the hair. It is unfortunate to find that in a book printed in 1962 no effort has been made to include references to the recent work of Mercer, Matoltsy, Zelicson and many other brilliant students of skin and hair. The reviewer considers these omissions most unfortunate because the work of these scientists will influence the course of future hair research for many years. It is refreshing, therefore, to find that Professor Astbury's chapter on the Molecular Structure and Elastic Properties of Hair has been almost completely rewritten since the fourth edition. This is in marked contrast to most other sections of the book, which received only minor revisions.

The sections devoted to permanent waving, artificial curling and hair dyeing are basically sound but full of minor errors and misconceptions. The emphasis on old fashioned singeing of hair is also surprising since the author states, correctly, "I can find no scientific proof of the value of this procedure." It is interesting to note that Dr. Saville agrees with the supposition that pityriasis simplex is the result of pityrosporum ovale infection. It is also surprising to find that, in a book of generally high scientific caliber, data on the tensile strength of hair by Leftwich (published in 1901) should be included along with similar inconclusive and amateurish data by the author.

The chapters concerned with the description, diagnosis, and therapy of various diseases of the scalp should have been brought up-to-date. Treatment of impetigo with neomycin is not mentioned; dandruff therapy with selenium sulfide is omitted.

This book suffers from the defect of wishing to be too many things to all readers. As a result, it is not valuable as a source book to the historian nor as a complete text for the chemist or physiologist, not adequate as a reference volume to the dermatologist, and not readable for the beautician or beauty operator (at whom a large portion of this book is directed).

The worst feature of this book is the unwillingness of the authors to separate clearly fact from fancy. Thus, the uninitiated is confronted with a babel of conflicting, contradictory and sometimes even erroneous statements. Only the knowledgeable expert is not confused by reading this book, and he might just as well save himself the trouble. —M. M. Rieger, Warner-Lambert Research Institute

Biological Research Method—An Introductory Guide, by H. H. Holman. Hafner Publishing Co., New York 3, New York. 1962. 262 pages. Price $5.75.

In these days of scientific emphasis, many a research beginner starts his work without adequate instruction in the fundamentals of experimental design. Usually the neophyte is tossed midstream into the laboratory current, and a considerable period of time has to be devoted to mastering the intricacies of good experimentation. All too frequently, however, appropriate planning techniques are not learned, and the result is a poorly executed experiment and worthless data. Dr. Holman has prepared a remedy for this major problem in an excellently written book that can best be described as a primer on experimental methods.

The author emphasizes statistical design and analysis of experiments. He also discusses in great detail the variables and considerations in-

volved in planning a biological experiment. Although the book is slanted toward agricultural experimentation, many of the topics are of general interest. The presentation of correlation and regression analysis, tests for homogeneity and goodness of fit, and the presentation of nonparametric methods serve as good introductions to these subjects. Such topics as selection of test animals, report writing, and proper presentation of data are also covered. References are numerous throughout, and both British and American sources are given.

The book, which could more appropriately be titled "Statistics Applied to Agricultural Experimentation," is written in a fresh and lucid style; and the reader should readily be able to transpose the suggested methods to his own field of interest. Dr. Holman's sense of humor is evident throughout. Typical is the quotation from Eisenhart and Wilson: "It has been alleged that certain people use statistics as a drunk does a lamp post—more for support than for illumination."

This volume should prove useful to young scientists at large, including those in the cosmetic industry who are just beginning to plan their own experiments.—J. F. Douglas and H. Breuer, Carter Products, Inc.

Topics in Organic Chemistry by Louis F. Fieser and Mary Fieser. Reinhold Publishing Corp., New York, N. Y. 1963. 668 pages, indexed. Price $10.00.

This, the latest of the Fiesers' texts on organic chemistry, is unmistakably a continuation of their earlier volume, *Advanced Organic Chemistry* (Reinhold, 1961). The first portion of *Topics* consists of nine chapters covering such diverse topics as Polynuclear Hydrocarbons, Alkaloids, Terpenoids and Dyes. Although the chapter headings in *Advanced Organic Chemistry* were clearly of a chemical nature, this distinction unfortunately could not be followed in *Topics*. Thus, chapters on Vitamins, Chemotherapy and Synthetic Polymers cover different and chemically unrelated subjects under the umbrella of headings drawn from disciplines other than organic chemistry. Despite this arrangement, which is used in almost all textbooks of organic chemistry, each chapter in *Topics* is readable and an excellent introduction to the chemistry of a wide variety of substances.

The chapter on Steroids, which is primarily descriptive, would have been strengthened by inclusion of a discussion of the stereochemistry of sterols. Similarly, the absence of physico-chemical material in the chapter on Synthetic Polymers seems unfortunate to this reviewer.

About 200 pages of this book are devoted to supplements to *Advanced Organic Chemistry*. This unique section contains several hundred entries covering literature published during 1961 and 1962 which the Fiesers believe worthy of addition to their earlier text. The selection appears to be excellent, and a glance through these pages, coupled with an occasional referral to *Advanced Organic Chemistry*, will be of value to all with an interest in organic chemistry. For example, if recent information on R and S specification of configurations, twistane, or components of royal jelly is of interest, a look into this section of *Topics* will prove helpful.

The style of *Topics* is lucid, and the structural formulas are neatly printed and carefully identified. Although essentially a textbook, *Topics* will prove to be a valuable and often-consulted reference for chemists who have been out of

school for some time.—M. M. RIEGER, Warner-Lambert Research Institute.

PHYSICAL AIDS TO THE ORGANIC CHEMIST by M. St. C. Flett. Elsevier Publishing Co., Amsterdam, New York. 1962. 388 pages, illustrated and indexed. Price $9.00.

This excellent book is intended to serve as an introduction to the field of instrumentation for the Organic Chemist. The book describes a number of well-known physical aids in sufficient detail to enable an Organic Chemist to decide whether they are applicable to his problems.

The scope of the book is best indicated by the titles of the chapters: Introduction, Chromatographic Separation, Gas-Liquid Chromatography, Zone Refining, Electronic Absorption Spectroscopy, Infra-Red Spectroscopy, Electron Spin Resonance Spectroscopy, Nuclear Spin Resonance Spectroscopy, Mass Spectrometry and X-Ray Crystallography.

The book is extremely well organized, the initial chapters dealing with the separation and purification of samples and the final six chapters with identification and structure diagnosis.

Each chapter has an introduction to the subject, a simplified discussion of the theory involved, a general description of each method and the technique and instrumentation involved; finally, stress is placed on the many applications and uses of the instruments.

The author demonstrates with many examples, tables and charts how the various physical aids can be useful in studying chemical structure, molecular shapes, bond energies, tautomerism, isomerism, complex formation, steric hindrance, hydrogen bonding, reaction rates, thermodynamic quantities, molecular weights, free radicals, impurities and other information of importance to the Organic Chemist.

Each chapter is well documented with an adequate list of references, which include original papers and a special bibliography of books on the subject. The type is large and clear, and the author's style of presentation is interesting and readable. The book has 109 figures and 38 tables. It is also provided with a subject index.

In summary, the book is an excellent review of the different instrumental techniques which can be utilized by the Organic Chemist to solve his problems and should be a valuable addition to his library.—S. R. KRAUS, Bristol-Myers

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SUBJECT INDEX TO VOLUME XIV

BOOK REVIEW INDEX TO VOLUME XIV

tatement required by the act of October 23, 1962; Section 4369, Title 39, United States Code, showing he ownership, management, and circulation of THE JOURNAL OF THE SOCIETY OF COSMETIC CHEMISTS, published six (6) times a year at 20th & Northampton Sts., Easton, Pa. 18043, for Volume XIV, Number 12 (December), 1963, filed on October 1, 1963.

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INDEX TO ADVERTISERS

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ACUTE EYE APPLICATION—ALBINO RABBITS

Each Chemoderm was tested in the rabbit eyes according to Draize, J.H.(5). Results: No eye responses of any consequence were produced. (11)

SKIN SENSITIZATION STUDIES—ALBINO GUINEA PIGS

A modified technique was used, Landsteiner, Jacobs (6), Draize, Woodward, and Calvery (7). Results: Unmistakable sensitization was not produced by any material tested. Possible sensitization was noted in three of six positive control animals, using known skin sensitizer. (11)

TISSUE CULTURE STUDIES, IN VITRO

Using human conjunctival cells (Chang) and primary explants of chick heart fibroblasts, cytotoxic studies were conducted. Results: The Chemoderms studied were tolerated at considerably higher concentrations than mercuric chloride and on a comparative tolerance level to that of oil of peppermint. (11) (12)

HUMAN SKIN PHOTOSENSITIZATION

Photodynamic Chemoderm studies were conducted using natural sunlight intensity 514.5 gram calories per square c.m. Challenge tests were conducted on the same skin site 3 weeks after initial exposure. Results: Chemoderms did not produce evidence of inflammation and/or pigmentation on either initial or challenge application. The control material produced inflammation and pigmentation. (11) (13)

REPEATED INSULT PATCH TESTING—HUMANS

Using 4 times the normal perfume level in cosmetics; procedures (Draize-Shelanski) Lehman, A. J., (8) and with patch modification (3). Results: No Chemoderm produced primary irritation, skin fatigue, or skin sensitization. (11)

USE PATCH TEST—HUMANS

Chemoderms were put in 6 nationally known and widely used cosmetics; cold cream, dry skin cream, hand lotion, four shades of lipstick, powder and make-up. Several hundred women under medical and dermatological supervision used the six cosmetics for three weeks. Fifteen days later they were challenge patch tested. Procedures: (11) (Traub-Tusing-Spoor) (9) Schwartz and Peck (10). Results: Initial and challenge patches revealed no evidence of primary irritation or skin sensitization. It is concluded that these substances can be considered safe for general use in consumer products. (11)

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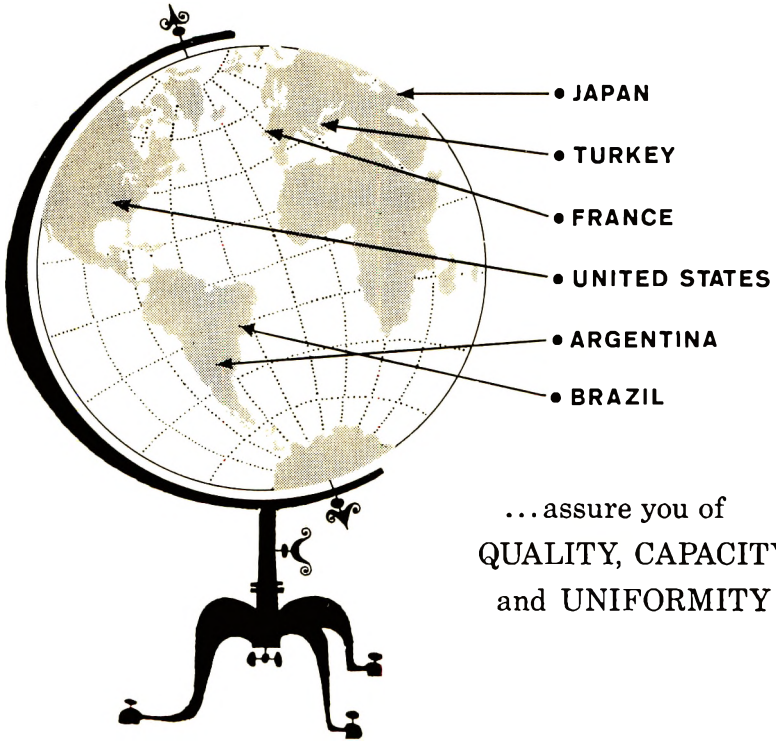

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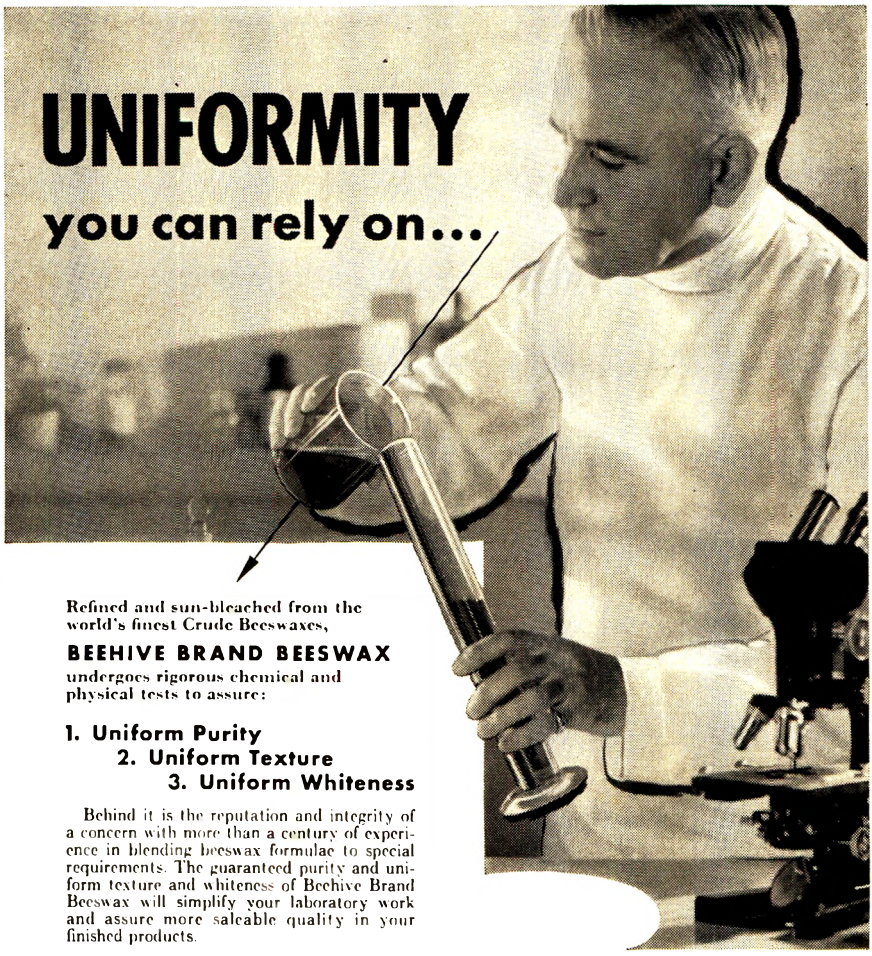

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