THE COSMETIC ASPECTS OF ESTROGENIC HORMONES

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A number of different cosmetic preparations containing estrogenic hormones have been on the market for some thirteen years. During this period of time, a substantial amount of clinical and other information has accumulated which bears either directly or indirectly upon the use of the estrogens in cosmetic formulations. In the following lines, an attempt has been made to review and to evaluate such evidence as is deemed to be relevant to the subject under consideration.

The Action of Cosmetic Hormone Creams Upon the Skin

Most cosmetic hormone creams, available on the market today contain from 7500 to 10,000 International Units (I.U.) of estrogenic substance per ounce of vehicle. This substance is usually of natural origin and consists essentially of estrone; smaller proportions of alpha-estradiol, equiline, and equilenin may be present in extracts from the urine of gravid mares which constitutes one of the most important sources of this material.

When applied in a cosmetic cream, this hormone potency may be safely regarded as being well below the threshold value for any systemic action. Assuming that a two-ounce jar of hormone cream with a total potency of 20,000 I.U. is used up over a period of one month, the individual daily application would contain 666 I.U. It is known, however, that absorption from an externally applied ointment does not take place to the extent of 100 per cent; at best, it is not greater than 40 per cent, and usually considerably less. Therefore, a maximum absorption of 290 units should be taken into account, which certainly is far less than required for any systemic effect. According to the *New and Nonofficial Remedies* (a publication of The American Medical Association), the therapeutic dose is 2000 to 10,000 I.U., by intramuscular injection, one or more times weekly, depending on the patient's response. As much as 50,000 I.U. per week may be required in certain cases. Of course, intramuscular injection results in a practically com-

plete absorption, in contradistinction to percutaneous application.

An experiment with a cosmetic hormone cream (containing 7500 I.U. per ounce) was conducted by Curth (1) on women ranging in age from 26 to 65 years. For a period of four weeks the hormone cream was applied to one thigh, and the cream without the hormone to the other thigh every day, preceded by cleansing with soap and water. The subjects did not know which cream contained the hormone principle. At the end of the four-week period, biopsies were performed on each of the areas treated.

The most constant finding was a succulence of the epidermal cells in the biopsies of the skin treated with the active cream.

Another experiment with the same cream formula was carried out by Traub and co-workers (2); as a control, the cream vehicle which did not contain the hormonal substances was used on the opposite side of each subject. Twenty-five women, ranging between the ages of 35 and 55, were selected for this experiment. They were given the hormone cream to use on the right side of the face, neck, and the right hand. The control cream was used on the left side of the face, neck, and back of the left hand. The subjects used the creams for a period of more than six months continuously. They were under the observation of a number of physicians, and a nurse was in constant charge of the experiment. None of the subjects confused the cream by using it on the wrong side.

At the conclusion of the experiment, twenty-four of the patients showed a greater improvement on the hormone-treated right hand, as compared with that on the left. In one of the cases, no difference could be noted between the two sides. Twenty-three of the women appeared to have improved more decidedly on the hormone-treated right side of the face and neck than on the left. In one, the opposite side appeared to be better. In one case no appreciable difference could be noted between the two sides. There were no untoward local effects whatever observed on the skin, or complained of during the course of the experiment, nor was there any evidence of systemic action, although no special study was undertaken to verify this point.

A comparative histologic study was undertaken using the original sections of skin, one from each hand, removed from the subjects prior to the onset of the experiment, and those from the same subjects at its conclusion. The dermatological interpretation of these findings may be summarized as follows:

1. The original section conformed to the histologic picture of the skin of the back of women's hands ranging between the ages of 35 and 55.

2. The final sections, both from the hormone-treated side and the control side showed that the use of the creams did not affect the epidermis.

3. It was possible from the histologic sections to differentiate be-

tween the active and the control sides.

4. The active side was recognized by observing various degrees of dilatation of the blood vessels, an increase in simple cellular elements, a greater succulence of the derma, as well as a betterment of the elastic tissue. There appeared to be no essential changes in the basophilic strands when the final sections removed at the conclusion of the experiment were compared with the original sections of the skin.

Gross examination indicated also a tendency toward the diminution of senile pigmentation or freckling.

Moreover, it could be shown by a comparatively simple experiment that skin areas treated with the hormone cream developed a greater avidity for taking up fluids (physiological saline) than the control areas.

In two more recent publications, Goldzieher (3) reported upon the topical application of hormone creams to senile skin. He used one preparation assayed at 10,000 I.U. to the ounce, and another one containing the synthetic estrogen, diethylstilbestrol (1 milligram per ounce).

With biopsies taken from both the treated and untreated areas (of the inner surfaces of the thighs and forearms) he found striking changes following a daily application of the hormone-bearing ointments over a period of six weeks. There was evidence of a regeneration of the surface epithelium. There were also significant changes in the mesoderm; thus the water content of the estrogen-treated site was greater, the number and size of the capillaries seemed increased, the bundles of collagenous fibers appeared less fragmented, and the elastic fibrils were more numerous. No such changes were elicited with the hormone-free ointment base.

It is argued that topical application of estrogens affects the skin to a much greater degree than oral or parenteral administration because by the latter modes of administration substantial amounts are lost for the skin through excretion, through inactivation by the liver, through attraction to the genital and mammary tissues, and through dilution by body fluids. In Goldzieher's opinion, the demonstrated absorption and utilization by the skin of topically applied estrogens opens a new field of therapy applicable to skin conditions not only induced by a hormone deficiency, but also to those involving other pathologic changes.

Jaffé (4) who reported earlier upon the treatment with follicular hormones of dermatoses of ovarian origin states that the stimulating effect upon the regeneration of the epithelium is in evidence also in the case of a healthy skin. He advocates, therefore, the application of a hormone cream in those cases (of flabbiness, etc.) where its positive action is likely to produce the appearance of a younger skin, owing to an improved skin tone and to an intensified capillary circulation. He indicates his awareness of the tem-

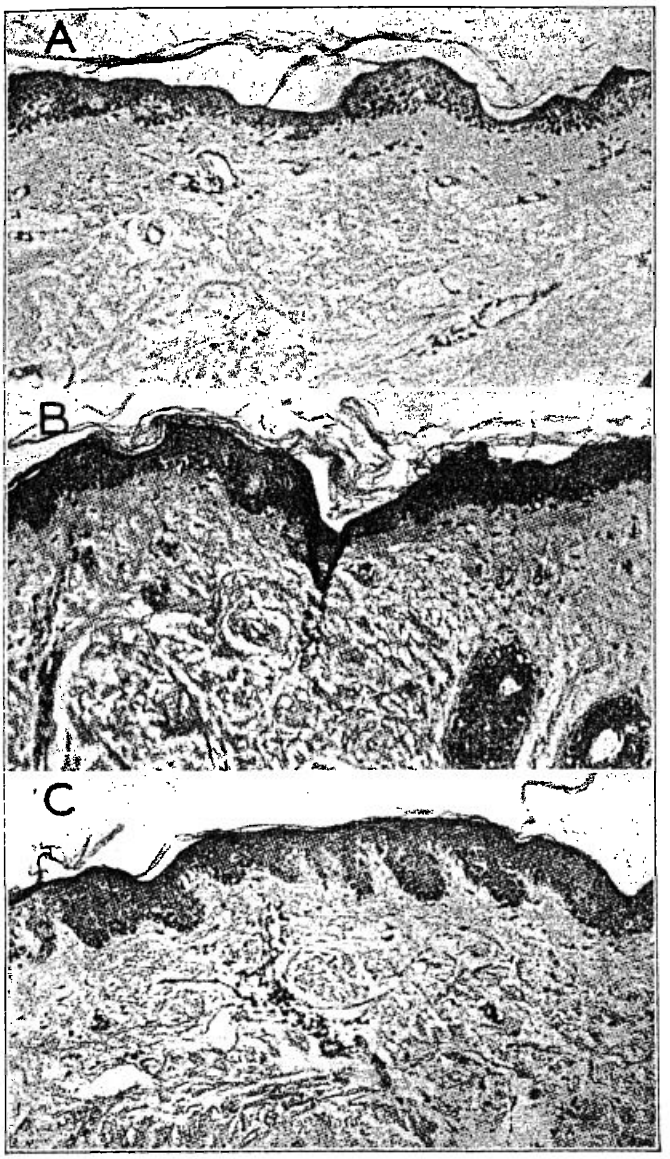

Figure 1.—Average response of senile female skin to continuous application of ointment containing 242 international units of estrogen per gram (7500 international units per ounce). *A*, Biopsy specimen of the skin of the back before treatment. Note the thin epidermis, the absence of pegs and the cuboidal cells of the basal cell layer; *B*, biopsy specimen of the skin of the back after application of an estrogen-free ointment for thirty days. There are thickening of the epidermis, greater cellularity and slight waviness of the basal cell layer; *C*, biopsy specimen after application of estrogenic ointment for thirty days. Note the increased sizes of the epidermal cells and the pronounced waviness of the basal cell layer, indicating proliferative activity.

(Reproduced from the paper by Eller and Eller in the *Archives of Dermatology and Syphilology*, **59**, 449 (1949).)

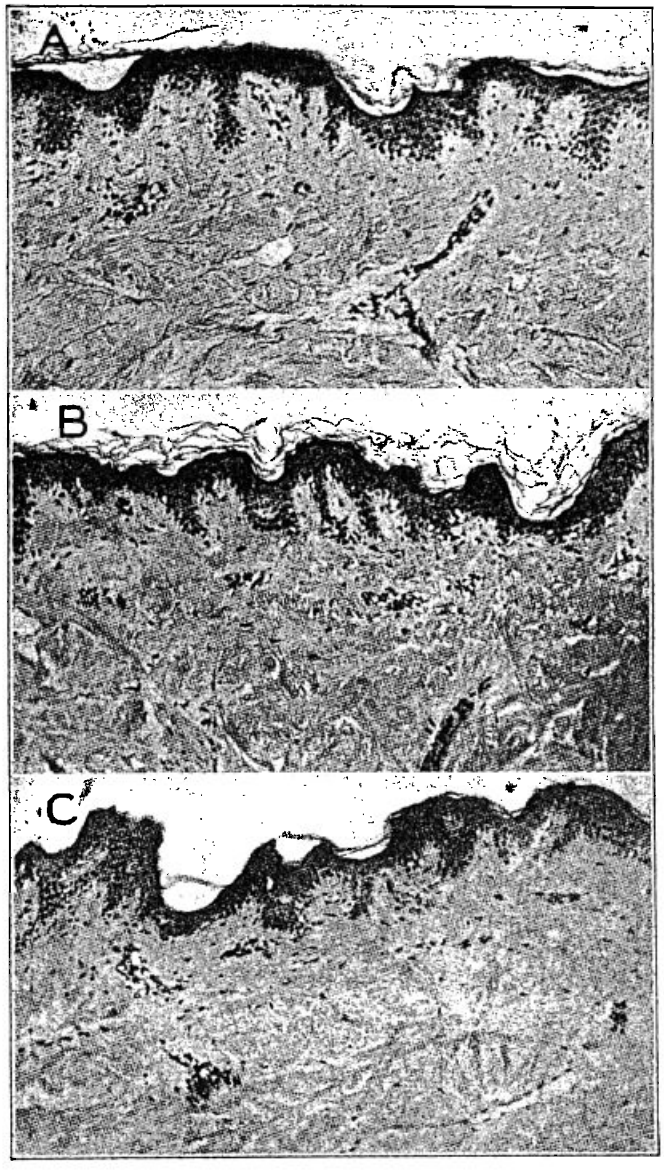

Figure 2.—Absence of response in skin of a young woman. *A*, Biopsy specimen from the skin of the back before treatment. Note the essentially normal epidermis with large, well-developed pegs and vesicular cells; *B*, biopsy specimen taken after inunction of estrogen-free ointment for sixty days. There is no perceptible change; *C*, biopsy specimen taken after inunction of ointment containing 242 international units of estrogen per gram. There is no difference between this and the control biopsy specimen.

(Reproduced from the paper by Eller and Eller in the *Archives of Dermatology and Syphilology*, 59, 449 (1949).)

porary character of this procedure by stressing the decline of its effectiveness upon the discontinuance of the application of the hormone cream.

An extensive investigation of hormone creams was carried out by Eller and Eller (5). It was found that estrogenic hormone ointments (with 7500 to 15,000 I.U. per ounce of excipient) produced consistent proliferative effects upon the skin epithelium (Fig. 1), the response varying with the age of the subject, the concentration of the estrogen, the duration of the individual application, and the total duration of the treatment; no epithelial response was obtained in the case of young women (20 to 30 years of age) who were free of any symptoms of endocrine dysfunction and who exhibited a fully developed epidermis of normal thickness (Fig. 2).

Definite histological changes were observed in all 19 post-menopausal subjects (aged 51 to 79) whose control biopsies showed senile atrophy with thinning of the epithelium. These changes were:

(a) the cytoplasm tended to increase in volume,

(b) the nuclei increased in size and assumed a rounded rather than ovoid form,

(c) the basal cell layer increased in waviness indicating proliferative activity,

(d) the epidermis gradually increased in thickness, and the epidermal pegs reappeared,

(e) the capillary blood supply became more prominent,

(f) the supportive elastic fibrillar structures became more pronounced,

(g) the elastic tissue and collagen (of the underlying corium) was affected only to a minimal degree.

The changes in the skin's epithelium reached a maximum at some time between thirty and fifty days; this maximum was attained more promptly with the large doses, and with the more prolonged periods of contact with the estrogenic material. They were maintained as long as the application was continued; omission of treatment caused reversion to the original atrophic condition.

There was a latent period of ten to twenty days before the appearance of a demonstrable effect.

Supplementary Illustrative Data

J. Goldzieher (6) studied the effect upon the senile skin of estrogenic (and androgenic) hormones applied by spraying (in the form of alcohol-ether solutions). While biopsies revealed distinct regenerative changes in the epidermis, his findings are of a lesser relevance to the consideration of the subject matter of this presentation, since the concentrations of the steroids employed were far above the physiologic range.

By way of supplementary information, reference is made to several selected papers which bear upon the general problem of local action of estrogenic hormones. It has been known for some time that topical hormone therapy gave excellent results in *kraurosis vulvae* and other regressive conditions of the

female genital tract. However, according to Fried and Goldzieher (7), estrogenic hormones stimulate also other epithelial structures, such as those of the mucous membranes of the nose and eyes; thus it was shown that the epithelial changes in *keratoconjunctivitis sicca* (Sjögren's disease) are affected favorably by topical estrogen therapy. Mortimer, Wright and Collip (8), as well as Ruskin (9), reported spectacular therapeutic results in atrophic rhinitis and ozena of the aged, following topical application of estrogens.

Goldzieher (3) found that the effect of estrogens applied topically goes further in the restoration of the physiological function of the epidermal cells, including correction of the abnormal process of keratinization which is characteristic of the senile skin and which accounts for its dryness and scaling. There was also an improvement in the clinical manifestations of these processes, notably in senile pruritus (of both sexes).

A high potency hormone cream was used by Shapiro (10) in treating a number of resistant cases of acne, with promising results. A combination of parenteral, oral and topical modes of administering estrogens was found by Drant (11) to be effective in the control of chronic, recalcitrant eruptions of a psoriasis-like character; recurrence of the cutaneous lesions, if treated at their inception, could be checked by topical application of a high-potency estrogen cream.

Ziskin (12) found topical estrogen therapy of value in treating certain atrophic changes in the buccal and gingival mucous membranes; Van Minden (13) used estrogenic hormones successfully in the treatment of chronic desquamative gingivitis.

The action of estrogenic hormones has been observed also on the skin of animals. Working with infantile and senile rats, Kun (14) found an increase in the thickness of both the epidermis and the corium; there was also an increase in the number of the oil glands. The blood vessels appeared dilated and the blood flow intensified. A dilatation of the blood vessels of the corium was observed also by Selye (15) on "rhino" mice, in addition to certain other local effects. The experiments by Reynolds and Foster (16) on the peripheral vascular action of estrogens, as observed in the ear of the ovarectomized rabbit, belong in this chapter.

Topical Versus Systemic Action of Hormone Cosmetics

All these findings indicate the logical need of assuming the existence of a direct action upon the skin of topically applied estrogenic hormones. Since the avidity of the different organs for materials of this type varies (the female genital system having the greatest capacity for attracting estrogen), it may well be assumed that the skin does not receive its due share following, e.g., intramuscular injection. This observation may be combined

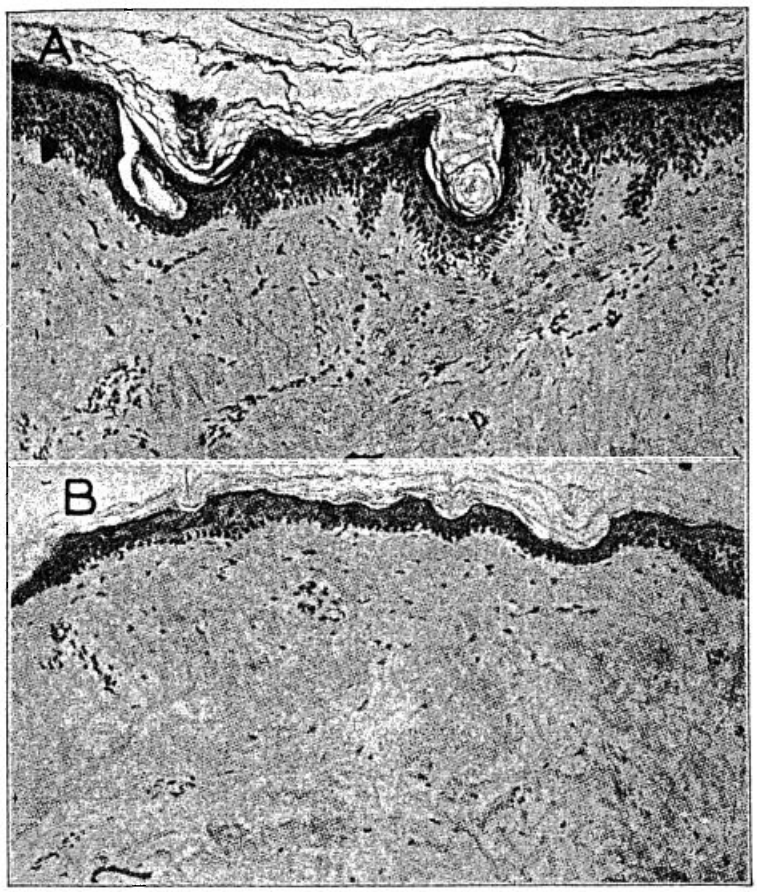

Figure 3.—Absence of cutaneous effects of systemically absorbed estrogen. *A*, Anterior surface of thigh after inunction of 484 international units of estrogen per gram. Regeneration and thickening of the epidermis have taken place; *B*, skin of opposite thigh after inunction with estrogen-free ointment only. There is no perceptible change, showing that neither estrogen-free ointment nor systemically absorbed estrogen has any cutaneous effect.

(Reproduced from the paper by Eller and Eller in the *Archives of Dermatology and Syphilology*, **59**, 449 (1949).)

with that referred to previously, *viz.*, that a major part of the estrogenic hormone applied percutaneously is not available for those organs which are primarily susceptible to estrogenic medication.

It follows from these considerations that if the hormone dose is below the threshold value for systemic action in the potential case of complete absorption, topical application is bound to result in an entirely local utilization, i.e., leaving practically nothing over for any systemic effect. Since the hormone potency of the properly formulated cosmetic

hormone cream is of an order of magnitude answering the above description, only a local and no systemic action might be expected.

There is direct evidence in support of the latter contention. Eidelsberg (17) carried out a series of experiments on a cosmetic hormone cream (of 7500 I.U. per ounce of natural estrogenic substance) with the specific purpose of ascertaining the existence of any variations in the estrogen content of the urine, and in the appearance of vaginal smears following the use of such a cream. He employed fourteen subjects who ranged in age from 18 to 56 years. The hormone cream, as well as a hormone-free control cream were applied nightly for three to four months. At the end of the experiment, no difference was found between the two groups with respect to the over-all pattern of urinary estrogen and of the vaginal smears. From this Eidelsberg concluded that in the amounts used and by the method applied, the estrogenic hormones did not produce any systemic effect.

Eller and Eller (5) whose work has been referred to previously, also report insignificant variations in the appearance of the vaginal smears of their subjects; from this they draw the conclusion that under the conditions of their procedure the absorbed estrogen affects the cutaneous epithelium directly, rather than *via* the systemic route. The postulate as to a direct, local action is borne out also by an *ad hoc* experiment in which the hormone cream was applied to one thigh, and the hormone-free excipient to the other; regeneration and thickening of the epidermis took place only in the former instance (Fig. 3).

Davis (18), too, is convinced that a cosmetic hormone cream containing around 7500 to 10,000 I.U. per ounce of estrone is unlikely to exert systemic action in view of the fact that the amount of estrogen absorbed by the skin is far below the level required to produce such an effect.

Of course, where the estrogen potency employed is substantially higher (as, e.g., in the several instances mentioned in the chapter headed "Supplementary Illustrative Data") the probability of combined topical and systemic effects must be considered. In such cases, however, the pertinent formulations are no longer of a cosmetic character; instead, they assume therapeutic functions in connection with the treatment of the particular pathological conditions involved.

Parenthetically, it might be added at this point that while the topical application of estrogens produces spectacular results in a number of instances, there exists a valid physiological and embryological reason for this phenomenon since the several varieties of tissue susceptible to the action of estrogens have the same embryonic derivation. Thus, while the vaginal mucosa or the endometrium is affected causally by estrogens it must be kept in mind that the skin represents but another developmental form of the same basic

embryonic tissue. Another causal connection between estrogenic hormone action and skin condition is evident from the frequent occurrence of atrophic skin changes during the menopause.

Are Hormone Cosmetics Dangerous?

Occasionally one encounters in the literature warnings as to the potentially carcinogenic action of estrogenic hormones. Their origin appears to stem from the experiments of Lacassagne (19) who showed that the administration of estrogenic hormones to young male mice from a cancer susceptible strain, increased the rate of cancer incidence in later life, as compared with the spontaneous cancer incidence of the controls. In the case of mice free from susceptibility to spontaneous mammary tumors, the treatment did not elicit such a reaction. Incidentally, in order to produce this phenomenon, Lacassagne had to employ doses which are many times higher than would correspond to those administered in the most intensive estrogen *therapy*, let alone in *cosmetic* usage.

The following random quotations are given in further reference to this matter:

Shorr (20): "Analysis of the data leads to the conclusion that no evidence exists that estrogenic hormones, given in physiological doses, have led to the development of carcinoma in man."

Geist and Salmon (21): "It is obviously impossible in human beings to administer the huge doses of estrogens over the long periods of time that would justify comparison with the experimental production of carcinoma in rodents. However, the conclusion seems warranted, on the basis of these studies, that, within the limits of the dosage used in this investigation (up to 53,400,000 I.U.) there appears no evidence to justify the fear that carcinoma of the genital tract may result from the therapeutic use of estrogens."

Hawkinson (22): "It is true that carcinoma can be produced in susceptible animals with estrogen. This would seem significant were it not for the fact that the work has been done chiefly in the rodent, with relatively huge doses, and with animals having a high hereditary tendency to the development of carcinoma."

Emge (23): "Evidence is accumulating to prove that the action of estrogenic hormones is controlled by definite biological patterns, and that their cancer-provoking faculty in small laboratory animals is strictly limited by hereditary tendencies. . . . We are not convinced, because estrogen favors spontaneous mammary cancer in mice highly susceptible to this malignancy, that other species of mammalia are likewise affected."

Goldzieher (3): "Warnings against the application of estrogens to the skin, lest they stimulate latent carcinogenic tendencies, are speculative, and not based on solidly established evidence. As a matter of fact, senile hyperkeratosis, including the pigmented variety, has

been classified with the precancerous lesions of the skin, yet it is favorably influenced by estrogens and may completely regress in the course of prolonged topical application."

Dodds (24): "(Lacassagne's results) do not constitute a contraindication to the clinical use of estrogens, since the doses given to human beings are fractional compared with those administed by Lacassagne to mice."

Eller and Eller (5): "Particular attention was paid to the cytologic character of the epidermal cells of the patients showing a response to estrogen. It can be stated unequivocally that no abnormalities were observed. There was no increase in the number of mitoses, or any suggestion of changes other than those of simple regeneration."

Davis (18): "An estrogen becomes a carcinogenic factor only when used on a strain of mice that have a strong hereditary tendency toward the formation of cancer."

Mazer and Israel (25): "The authors have observed the development of uterine cancer in only 2 of 1000 climacteric women who had received as much as 10,000 rat units of estrogen every fourth day for periods varying from six months to two years. According to the law of averages, more of these patients will eventually develop breast or uterine cancer, but its relationship to estrogen treatment of two or more years previously would be more than doubtful."

Dunbar (26): "There has been a considerable amount of work on the carcinogenic properties of these materials. In highly susceptible strains of rats under very special conditions, the administration of the estrogens has apparently produced carcinoma, but with ordinary laboratory animals and in all studies so far on human beings there is no evidence whatsoever that these products are carcinogenic. . . . "We have investigated the files of a number of firms producing these products searching for evidence of injuries. We have not found such evidence."

The latter reference deserves particular attention since it is based upon information gathered by the Food and Drug Administration.

It should be noted, in this connection, that no quantity of estrogen administered for therapeutic purposes can produce a concentration in the blood stream comparable to that during the second half of gestation. As shown by Salter, Humm, and Oesterling (27), also by Jailer (28), the excretion of natural estrogen in the urine of the normal female, at its peak, amounts to an estrone equivalent of 600 to 1000 I.U. daily. (Between the peaks the variation is from 50 to 200 I.U. daily.) Nevertheless uterine and mammary carcinomas do not occur in childbearing women more often than in nulliparous women of the same age and hereditary background.

In any case, because of the great difference in the comparative sizes of dosage, it is hardly admissible to consider the relevance of the carcinogenic aspects of estrogenic hormone

therapy to the *cosmetic* application of these materials. The cosmetically applied "dose" of a correctly formulated hormone cream is but a fraction of the "therapeutic" dose; whereas the latter is administered to produce systemic action, affecting particularly the functioning of the feminine gonadal apparatus, the former almost surely is without any systemic action, its effect being topical and restricted to the skin. In this latter connection reference may be made to a statement by Schwartz (29) to the effect that "The Section of Dermatoses Investigations of the U. S. Public Health Service has no record of skin damage resulting from the use of hormone creams."

Cosmetic hormone preparations have been on the market for over thirteen years during which time millions of jars have been used by the consuming public. There is no published or other medical record as to any harmful results attributed to the use of properly compounded hormone cosmetics.

Regulatory Aspects

There exists no federal state or municipal regulation or ordinance prohibiting the sale of hormone cosmetics. True, there have been several instances of some restraining action being considered; however, upon investigation of the pertinent evidence, such action was either dropped directly or it resulted in some form of amended procedure. Thus the New York State Board of Health which, some time ago, had started to restrict the sale of hormone creams, dropped its action to this effect. The states of Virginia, Kentucky, and Massachusetts rescinded their proposed restrictive regulations upon review of the facts involved. Perhaps the most publicized case is that of the State of Louisiana which terminated with the promulgation of the following regulation:

"No cosmetic or beauty preparation containing as one of its ingredients estrogenic hormone, or any of its derivatives, or any synthetic chemical product possessing properties similar to those of estrogenic hormone, may be manufactured, processed, packed, sold, or distributed in Louisiana unless its label bears adequate directions for use and a statement of the quantity, in units, of such products."

As to the labeling of hormone cosmetics, it must be borne in mind that their mode of action is such as to make them fall in the category of drugs (in addition to that of cosmetics) within the definition of the term "drug" given by the Federal Food, Drug and Cosmetic Act. This classification calls (among other things required by this statute) for a statement of the active ingredients upon the "labeling" of the hormone-bearing product. If the latter is to be sold in a state or a country having special labeling or selling requirements, due cognizance must be taken of them before placing the product on the respective market.

Conclusion

While there are some differences of opinion as to the exact *modus operandi* of the topical action of estrogenic hormone cosmetics, it appears to be well established that their positive effect is one of improving the appearance of the aging skin, and that this effect is produced by a local rather than by a systemic action.

Evaluation of pertinent data does not disclose any health risk attaching to the regular use of properly formulated cosmetic hormone preparations.

Hormone preparations with a potency of 7500 to 10,000 I.U. per ounce produce satisfactory cosmetic results. The use of preparations with higher hormone potencies for cosmetic purposes appears to be neither necessary nor justified at this time.

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