PERFUME DERMATITIS

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IN THE CASE of skin reactions by perfume materials, one is concerned, as a rule, with phenomena in the category of allergic hypersensivity rather than in that of primary irritation.

Allergic sensitivity to perfume, like any other form of cosmetic allergy depends upon a variety of factors. Thus, certain types of skin are more likely to respond with manifestations of sensitivity than others.

While protein participation is usually involved in antigenic action, various substances, other than proteins, can act as antigens. In fact, some simple organic chemicals can produce sensitization phenomena, following intracutaneous injection or topical application to healthy skin.[1-5] The capacity of a simple substance to act as an antigen is assumed to depend upon its combining ability whereby an originally "native" protein becomes "foreign" and therefore antigenic.

SENSITIZATION STUDIES

This is relevant to a brief but highly significant report by Landsteiner and Jacobs in the matter of a perfume material, viz., methyl heptine carbonate. Some time ago, H. L. Baer[6] connected a case of lipstick dermatitis with the occurrence in the lipstick perfume of methyl heptine carbonate. Similar findings were made by Hoffman and Peters,[7] as well as by others. Alerted by these reports, Landsteiner and Jacobs[8] carried out a series of sensitization experiments which proved that guinea pigs could indeed be rendered specifically sensitive to this chemical, following several exposures at weekly intervals to its dilute solution in olive oil, either in the form of an intracutaneous injection or in that of an inunction of the unbroken skin. The specificity of the imparted sensitivity was evidenced by the failure of other chemicals possessed of marked sensitizing capacity e.g., 2, 4-dinitrochlorobenzene, 2-4-dinitrobenzylchloride, o-chlorobenzylchloride to produce any significant reaction upon the skin of the sensitized animals.

Although no attempt was made to demonstrate any reaction *in vitro* between methyl heptine carbonate and a protein, Landsteiner and Jacobs assumed that the former chemical was made to react *in vivo* with some protein so as to effect the latter's conversion into a specific antigen.

While the above is an example of singular specificity in sensitization there exists also a group specificity which is evidenced in the case of chemically related substances capable of giving rise to antigen formation.

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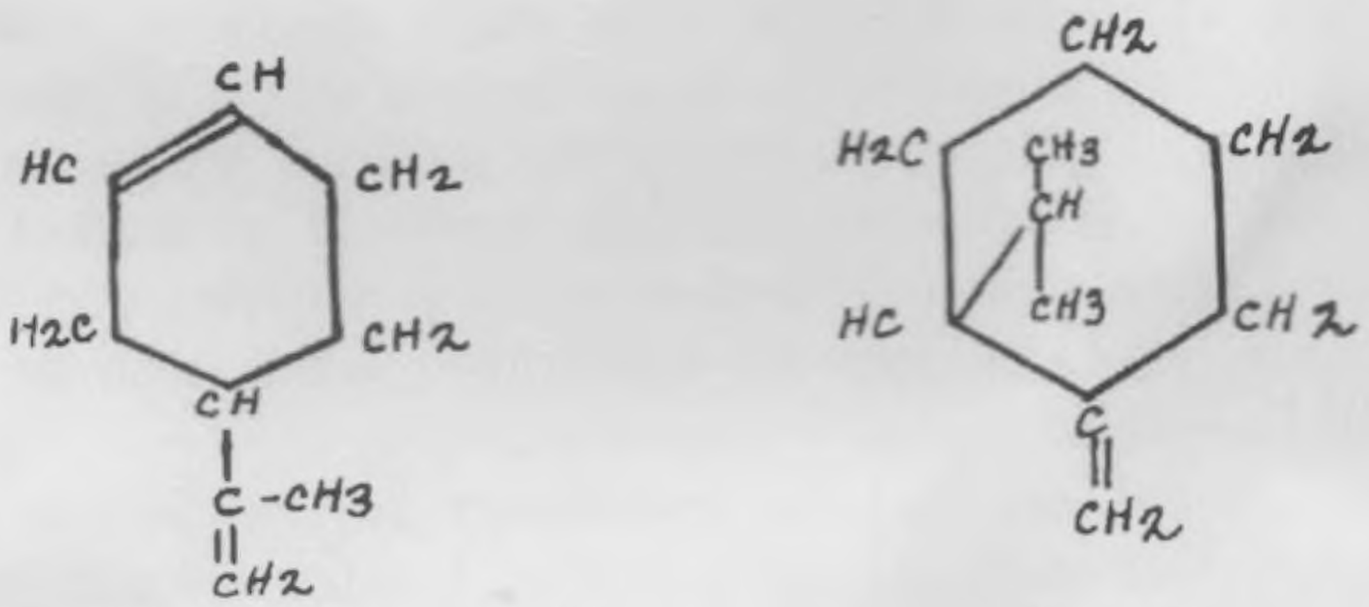
In other words, if sensitization is achieved by a particular substance, a dermal reaction may be elicited by another substance structurally related to the sensitizer

The latter is relevant to another series of highly indicative experiments carried out by Keil.[9] His interest has been attracted to this problem by some cases of dermatitis attributed to citronella oil which already had a record of inciting dermatitis in susceptible individuals.[10] The patient who was found originally to be sensitive to citronella oil was now patch-tested with oil of lemon again he responded with a positive reaction. In an endeavor to ascertain the offending principle, Keil applied one per cent solutions of several constituents of citronella oil he obtained strongly positive reactions with citronellal, and weaker positives with citronellol, citral geraniol and geranyl acetate. The same results were obtained in two other cases.

In order to make sure that the patch test results were due to specific sensitization, Keil applied lemon oil as well as the several single compounds listed to twenty-six control subjects afflicted with different skin ailments totally unrelated to the citronella oil type of dermatitis. Negative responses were obtained in twenty-three cases, and mild positive responses in three cases. This finding tends to support the postulate of specificity of the substances tested.

One of Keil's patients, who was sensitive to oil of lemon, was found to give a positive reaction also with oil of turpentine. Because of this, tests were run on this individual with solutions of *alpha*- and *beta*-pinene. Positive reactions were obtained with both isomers, *beta*-pinene being by far the stronger agent. The latter is a close chemical relative of limonene this furnishes the explanation for the sensitivity to both lemon oil and turpentine.



Limonene **Beta-pinene**

Fig. 1. Structural formulas of limonene and *beta*-pinene.

In comparing the structural formulas of limonene and *beta*-pinene, one observes that both have an exposed methylene radical their reactivity resulting in eventual sensitizing action might well start at this point.

It was mentioned previously that the aldehyde citronellal appeared to

act as the primary allergen of oil of citronella. The synthetic hydroxycitronellal also produces a positive reaction although somewhat weaker The unsaturated alcohol citronellol is a strong reactant possibly because of its similarity to citronellal with regard to the end position of a methylene group which is found also in the case of limonene and *beta*-pinene. By contrast, geraniol gave only a weak reaction in spite of its unsaturated character and this was true also of citral which is in the same relation to geraniol as citronellal is to citronellol the reason is possibly to be sought in the substantial absence of a reactive methylene end group in geraniol as well as in citral.

$$H_2C=CH(CH_3)\bullet CH_2\bullet CH_2\bullet CH_2\bullet CH(CH_3)CH_2\bullet CH_2OH$$
Citronellol

$$H_3C\bullet CH_2\bullet CH_2\bullet CH_2\bullet CH_2\bullet CH_2C(CH_3)=CH\bullet CH_2OH$$
Geraniol

In addition to the relationships between chemical structure and sensitizing action of some individual compounds, Keil's work suggests the existence of group reactivity in that persons sensitive to oil of citronella may be equally unable to tolerate exposure to the essential oils extracted from the other members of this botanical family such as the oils of lemongrass, palmarosa, and gingergrass. However the cross sensitivity may extend to oils of unrelated botanical origin whose chemical composition bespeaks their reactivity such as oil of *Eucalyptus citriodora* consisting almost entirely of citronellal

A reported case of dermatitis caused by oil of geranium[11] probably belongs in this chapter also a case of cheilitis due to the presence of geranium oil in a lipstick perfume.[12] Some evidence points to the reduced sensitizing action of terpeneless oils.[13]

DIGEST OF PERFUME SENSITIVITY DATA

Unfortunately only a very few papers have been published permitting a systematic insight into the subject of our discussion. Most of the other papers are essentially case reports identifying perfume or perfume ingredients as sensitizing agents, or else some "wholesale" reports of tests performed in a manner virtually precluding either theoretical or practical utilization of the information obtained.

Following are some reports belonging in the former category

One of the earliest papers by Freund[14] deals with the so-called Berlocque dermatitis, a condition attributed to the use of the classic type of Eau de Cologne. The inciting agent appears to be bergamot oil. However Berlocque dermatitis and the concomitant skin pigmentation are not the sequelae of a simple sensitization, but rather the results of a combination of factors in which irradiation by sunlight plays an essential role. This condition has been observed and reported upon by several investigators, both in this country and abroad.[15-21] Rogin and Sheard suggested that

chlorophyll or some adulterant may be responsible,[22] but this is not in agreement with the findings of Giraudeau and Acquaviva[23] who definitely exclude chlorophyll and linalyl acetate as causative agents, although they did demonstrate that oil of bergamot sensitizes to visible light within the range of 3900 to 6000 Angstrom units, i.e., from the violet to the yellow part of the solar spectrum. According to Goodman[24] the presence of traces of copper in the oil, originating from the shipping containers made of copper is necessary for the sensitization reaction to take place. Recent experiments by Lerner Denton and Fitzpatrick[26] indicate that it is the psoralens present in a variety of natural essential oils (including bergamot oil and other citrus oils which are responsible for the hyperpigmentation of Berlocque dermatitis.

An interesting observation by Urbach and Kral deserves mention at this point, viz., that internal ingestion of vitamin C prevents photosensitization by oil of bergamot.[27]

It is known now that oil of bergamot does not stand alone as a factor in photodermatitis. Other essential oils, both of the citrus type as well as those belonging to other categories, have been recognized as photosensitizers. Among them is oil of lime which causes pigmentation upon exposure to sunlight. As shown by Sams,[25] the pigmentogenic action appears to reside in the longer wavelengths of the ultraviolet radiation, ust below the zone of visible light 3100 to 3700 Angstrom units While the nature of the photocatalytic agent remains undetermined, doubt is raised as to the participation of copper as suggested by Goodman in the case of bergamot oil, since the reaction is produced with freshly expressed or extracted oil.

Oil of neroli is a photosensitizer as is oil of petitgrain.[28] Although of lesser significance in perfumery oil of cedarwood acts in a similar manner producing a photosensitization type of dermatitis,[29] sometimes associated with pigmentation.[30]

Oil of lavender has been identified by Finkenrath[31] as the cause of simple sensitization dermatitis without exposure to light being necessary) and pigmentation of the skin following topical application has been reported by Szanto.[28]

Other essential oils suspected or accused of sensitizing capacity are the oils of rosemary angelica, cassia, calamus, eucalyptus, orange, anise, bay bitter almond, cade, ylang-ylang, carrot seed and linaloe·[32] with respect to the last-named oil, the capacity for sensitization may reside with *l*-linalool which, like the sensitizing citronellol, has the methylene group in an end position

$$H_2C = CH(CH_3) \cdot CH_2OH \cdot CH_2 \cdot CH = C(CH_3)_2$$
l—Linalool

Of course, mention of photodermatitis is made here only with direct reference to the participation of the several essential oils in this picture. However this is not deemed to be the place for dealing with the much

broader aspects of photodermatitis, or even with the more limited aspects of phytophotodermatitis.

If one concedes that essential oils may act as irritants, then Peck's[33] observations are relevant to the phenomenon of pigmentation, since it has been shown that the latter can be produced without the contributory factor of sunlight.

As to oil of orris, it seems that most objections to its use stem from the well-recognized allergenic character of orris root which, in dried and powdered form, had been used, some time ago, as an ingredient of face powders and other cosmetics. However no cases of allergy appear to have been reported as being directly associated either with oil of orris or with orris concrete.

The selective action of an essential oil in creating a limited area of dermal response to its sensitizing effect has been reported by Cummer.[34] His patient was in a habit of dropping some cinnamon-flavored liquid dentifrice in the palm of his left hand, and picking it up with a tooth-brush the excess was allowed to run off between the fingers to the dorsum of the hand. An erythemato-vesicular eruption occurred in the interdigital spaces of the hand, but at no time was there any evidence of irritation of the mouth, lips or face. Patch testing with the ingredients of the dentifrice confirmed the causal involvement of oil of cinnamon and, incidentally elicited a mild positive reaction to oil of spearmint.

Some perfume materials have the bad reputation of being irritants or sensitizers, although the pertinent information appears to be more putative than experimental or clinical in character This comment applies, e.g., to eugenol and isoeugenol, concerning which little directly applicable information is available.[35-37] Incidentally isoeugenol (4-propenyl guaiacol) is thought by some to be less of an offender than eugenol,[38] while others would like to see its use avoided.[39] Since both eugenol and isoeugenol are phenol derivatives of comparatively low molecular weight, it is conceivable that in concentrated form they might have a direct or primary untoward effect upon the skin the same would be true of the carnation or spice type of perfume compositions in which either or both might occur It is questionable, however whether this has any direct relevance to their employment in scents for creams, soaps, et cetera. Reference has been made above to the molecular weight of phenol derivatives, because it is known that the toxicologic action in the series of phenol homologs decreases as their molecular weight increases.[40]

Heliotropin has been implicated as a possible cause of dermatitis[41] and its use in lipstick perfumes is being discouraged.[42] Skin irritant action has been attributed to methyl anthranilate.[42]

A somewhat special position is occupied by oil of wintergreen, consisting substantially of methyl salicylate, because of its ready penetration through the skin. According to Macht[43] and Harry[44] however this oil is not

unique in its penetrating capacity other essential oils, too, are effective penetrants with a potential for physiologic or pathologic effects.

There are also some case reports of reactions to finished perfumes. Thus, Tobias[45] mentions one such case in which a well-known perfume caused dermatitis after prolonged usage. In connection with this case, he stressed the applicability of the antigen-antibody principle in view of the occurrence of an incubation period of six months which finally ended with a cutaneous display of acquired hypersensitivity A case of dermatitis attributed to a jasmine bouquet type of perfume was reported by Bloom.[46] In this case, the offending agent was found to be benzylidene acetone. Von Varga[47] presented a case of hypersensitivity to a hyacinth perfume. A report by Feiler is interesting as well as amusing because, in this case, the offending perfume was one distributed by a house specializing in "hypoallergenic" cosmetics.[48]

The type of paper referred to before which offers but little by way of utilizable information is that by Patterson and Hall,[49] subsequently expanded by Katz.[50] These papers merely list a whole series of essential oils and aromatic chemicals which were applied either in pure form or in the case of crystalline substances in the form of saturated alcoholic solutions, under a closed patch, to the inner portion of the lower arm. The results indicate at best that most of the essential oils and aromatic chemicals tested should not be regarded as primary irritants, although some of them did produce a skin reaction in isolated instances. In some cases, as, e.g., in that of methylnonylacetaldehyde, a cutaneous reaction may appear in one to five days following application. It is regrettable that this type of study has not been enlarged in scope certainly a single application of a number of undiluted perfume materials to the human skin bears hardly any relevance to the problem with which one is concerned here.

ALLERGENIC EFFECTS OF INHALED PERFUMES

A special position is occupied by the allergic phenomena elicited without direct exposure of the skin to the sensitizing action of perfume or of perfume ingredients. It is well known that inhaling the perfume of certain flowers, such as roses or lilac, may cause sneezing or rhinorrhea in sensitive individuals, and there is adequate evidence in support of the contention that this is due to some volatile components of the floral oil rather than to pollen.[51] Urbach[52] demonstrated the existence, in some cases, of a purely nasal hypersensitiveness to the essential oils of lemon, orange and tangerine also to oil of pine needles without any concomitant cutaneous response in other cases, nasal and cutaneous reactions were found to run parallel.

Evidently infinitesimal traces of some odoriferous materials possess the allergenic capacity of eliciting both respiratory and dermal responses. Very little pertinent information has come to light from the field of perfumes although, judging by the observations reported with other odorous

materials, this type of hypersensitivity should be encountered more commonly As to some of the related phenomena, reference may be made here for illustrative purposes to the reported cases of a hypersensitiveness to the inhaled aroma of coffee[52] and of certain vegetables[53] producing respiratory or cutaneous symptoms.

It is of possible interest that, in one case of hypersensitivity to the perfume of locust blossoms, desensitization of the patient could be effected by feeding of a seventy-two hour enfleurage of these blossoms in lard over a period of two weeks. This procedure prevented the severe "hay fever" symptoms from which the patient had been suffering previously in spite of almost continuous exposure as occasioned by living in a locust grove.

DISCUSSION

The several instances presented here may furnish an idea as to the probable size of the field yet to be explored. By way of giving just a few examples of what needs to be learned, one might point to the very small number of perfume materials studied to date for their irritant or sensitizing potentials, and of the concentrations in which these potentials become manifest in the form of clinical dermatitis. In this connection, hardly anything is known concerning the existence of sensitizing synergisms or antagonisms of groups of perfume materials floral and essential oils, aromatic synthetics, et cetera which are, of course, the fundamental entities of all perfume formulas. Next one might stress what must be a marked difference between the transitory or fugitive effect of the application of a perfume or toilet water on one hand, and the fixation of a perfume to the skin by means of some vehicle such as a cream, a lipstick, a face powder et cetera, on the other Furthermore, hardly anything is known concerning the influence of the various cream and emulsion types upon the dermal effect of the many perfume ingredients with which they may be scented in this connection, there come to mind studies on skin absorption such as those carried out by Harry[44] which might well lend themselves for adaptation to the problem under discussion, especially in view of his finding that certain essential oils show the greatest capacity of skin penetration, greater than that shown by the most active vegetable and animal oils or fats studied. And what about the possibility of a contributory effect of perfume in the case of cosmetics with admitted dermal action, such as antiperspirants? Since soaps and detergents are now known to affect skin morphology and physiology what added effect is produced by the perfume in these vehicles, and how should one select a perfume for them? The number of open problems is really legion.

In his endeavor to eliminate allergenic or sensitizing ingredients from his formulas, the cosmetic chemist has been, on the whole, quite successful. However the perfume presents a problem both *per se* and as a component of cosmetic formulas there is a general feeling that, where cosmetic sensitivity is encountered, perfume is quite likely to be involved.

The evidence in this matter may appear to be more indicative than supportive at the present time. The reason for this is to be sought in the dearth of published relevant information probably due to the comparative mildness and transitoriness of the dermal symptoms offering but a moderately interesting stimulus to the dermatologist who is more likely to be attracted by true skin pathology as an object of study The complexity of the perfume formula is also apt to act as a deterrent. Nevertheless, a first corrective step appears to have been taken recently in the direction of creating perfumes with a low sensitizing index, through the selective use of components essential oils, chemicals, resins, et cetera which have been specially purified, and screened by patch tests for their fitness to serve in such perfume formulas.[54]

Some pertinent comment may be in order here on the subject of "hypoallergenic cosmetics." To the extent that in its strict meaning this term implies freedom from acknowledged or suspected allergenic agents, it could probably be applied to any cosmetic preparation formulated by an informed chemist and produced under proper sanitary manufacturing conditions. Yet cosmetics marketed specifically under the "hypoallergenic" designation are usually made available perfumed as well as unperfumed, with an increasing trend toward the latter type as fostered by some dermatologists and allergists who have become aware of the perfume's capacity for sensitization, and who now wish to exclude this apparently significant source of allergic reaction, when indicated by the patient's relevant condition.

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Submitted June 5, 1957

USE OF PENICILLIN FOR MASTITIS

"The Federal Food and Drugs Administration is enforcing new regulations regarding penicillin in mastitis ointments.

"The new regulations require that no single dose of mastitis ointment can carry more than 100,000 units of penicillin. Formerly, some ointments contained as much as one and one-half million units per dose.

"The reason for the regulation is that a recent Federal Food and Drug survey indicated that too high a percentage of market milk contains penicillin. Unless this percentage is reduced, the antibiotic agent will be banned in mastitis ointments.

"The regulations also state that every ointment tube label must warn dairymen to withhold from market for at least three days all milk from treated cows. It takes at least 72 hours for the penicillin to work its way completely out of the udder *The Farmer's Digest*, January, 1958.