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Journal of the Society of Cosmetic Chemists

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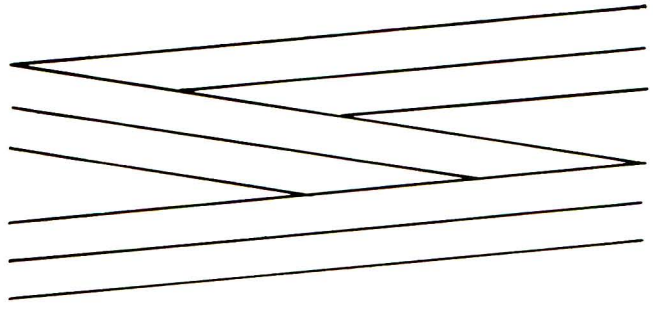

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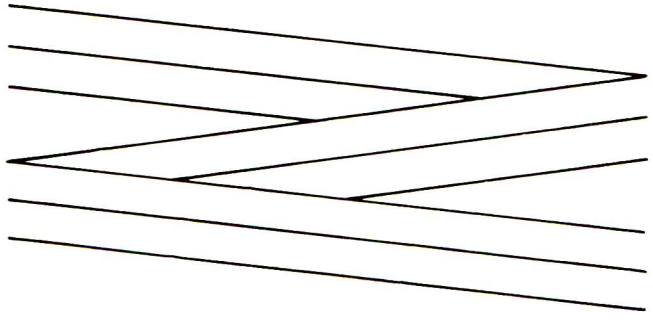

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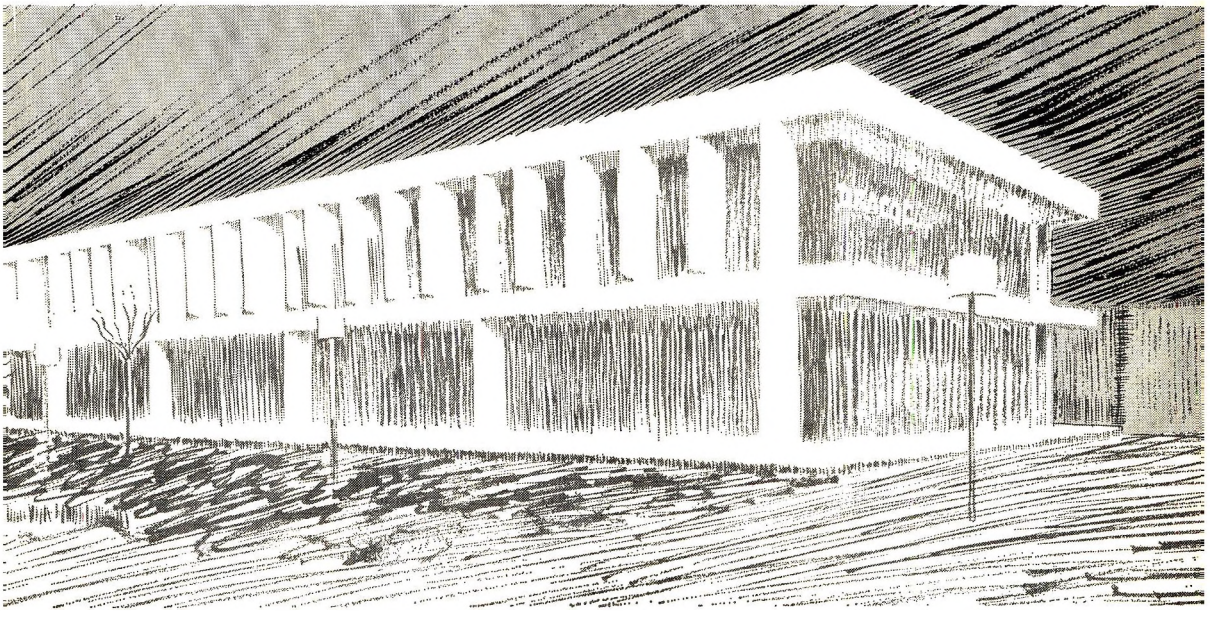

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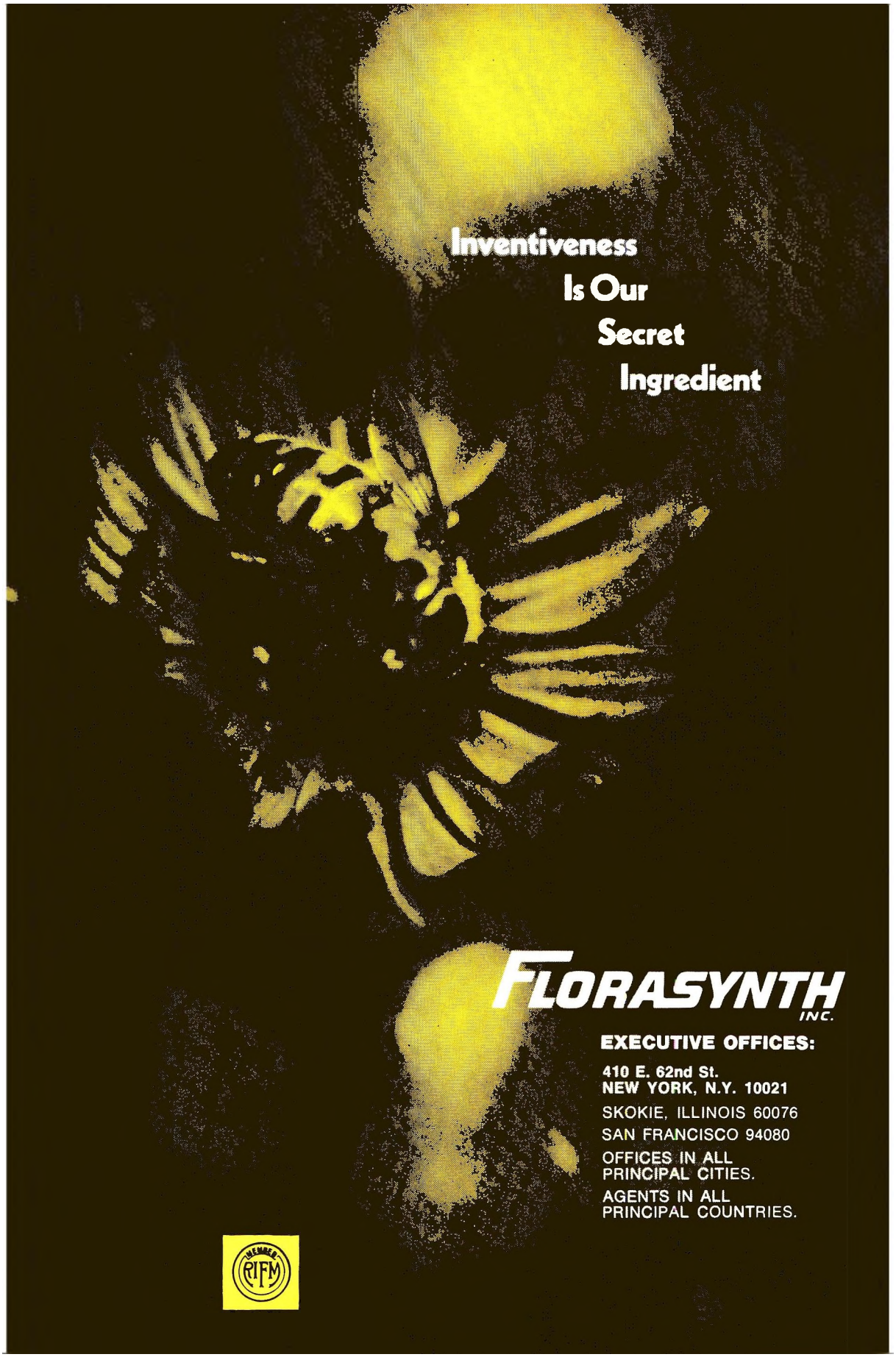
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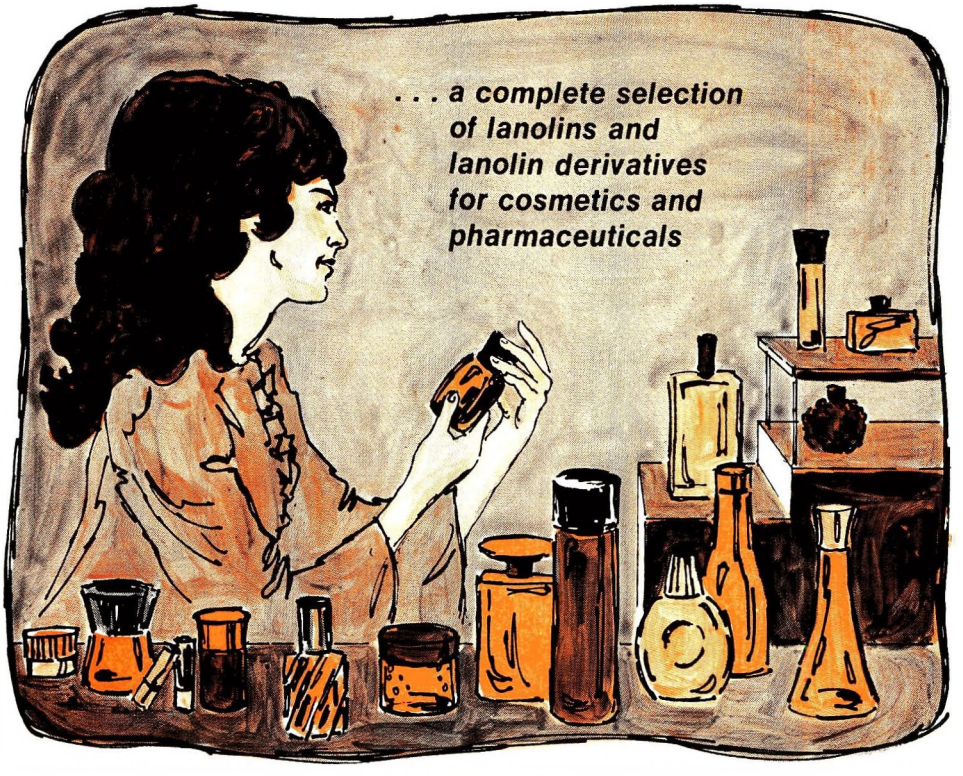

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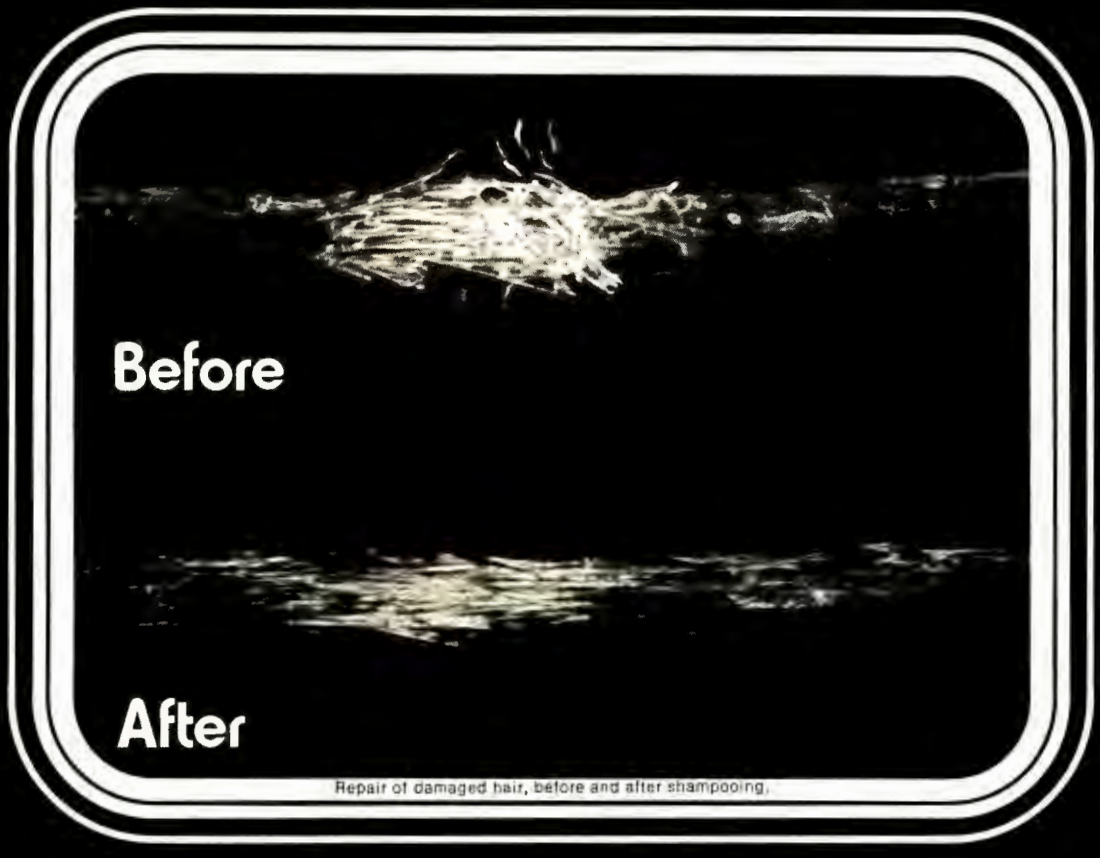

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SYNOPSES FOR CARD INDEXES

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

Some problems on the appraisal of the skin safety of hexachlorophene: Fujio Morikawa, Toshiaki Kobayashi, Yasuhisa Nakayama, Yoshiko Yokoyama, Minoru Fukuda, Shinobu Katoh, and Toshiaki Nagura. *Journal of the Society of Cosmetic Chemists* **25,** 113 (March 1974)

Synopsis—The safety of the bactericide hexachlorophene for use on the skin has been questioned in recent years. The authors have investigated primary irritation, contact sensitization, phototoxicity, and photosensitization with this chemical on animals. Results confirmed that hexachlorophene showed a higher degree of primary irritation than any other halogenated compound tested in this study. Irritation from this chemical increased with time and reached a peak 96 to 120 hours following application. Moreover, there was a difference in the irritant reaction to this chemical depending upon the solvents used.

In another study, photopatch tests of hexachlorophene were performed on guinea pigs and rabbits. A greater inflammatory reaction was observed at the irradiated site, as compared with the control site which had been treated topically with the chemical but without exposure to ultraviolet light. In addition, histological examination revealed disturbances of blood vessels apparently caused by topical application with hexachlorophene.

Oxidation dyes: mechanism of formation and structure: Hans Husemeyer. *Journal of the Society of Cosmetic Chemists* **25,** 131 (March 1974)

Synopsis—The reaction of 1,4-diaminobenzene with derivatives of 1,3-diaminobenzene in ammoniacal aqueous hydrogen peroxide solutions was investigated. The initially formed quinonediimine couples with other components to yield dyes of the toluylene blue type which was discovered by O. N. Witt. The entire group of dyestuffs was synthesized by systematic changes of the substituents. Their spectral behavior and their rate of oxidation to phenazines at elevated temperature permit interesting insights into the positions of the mesomeric basic state.

The evaluation of antiperspirant efficacy—influence of certain variables: Paul A. Majors and John E. Wild. *Journal of Society of Cosmetic Chemists* **25**, 139 (March 1974)

Synopsis—Antiperspirant activity estimated by a gravimetric procedure is discussed. The possible influence of several factors on observed effectiveness are evaluated, namely, sweating rate, axilla treated, sweat collection conditions, and method of data analysis employed. Panelist-to-panelist variation in response is briefly discussed.

The commission of sin through the medium of the skin patch test: Earle W. Brauer. *Journal of Society of Cosmetic Chemists* **25**, 153 (March 1974)

Synopsis—The skin patch test is a valuable instrument. In the hands of well-meaning, but misguided, individuals the power of this instrument is creating significant problems for medicine in general and for the cosmetic industry in particular.

J. Soc. Cosmet. Chem., **25**, 113–130 (March 1974)

Some Problems on the Appraisal of the Skin Safety of Hexachlorophene

FUJIO MORIKAWA, M.D., TOSHIAKI KOBAYASHI, B.S., YASUHISA NAKAYAMA, B.S., YOSHIKO YOKOYAMA, B.S., MINORU FUKUDA, B.S., SHINOBU KATOH, B.A., and TOSHIAKI NAGURA, B.S.*

Presented May 26, 1972, Seminar, Los Angeles, Calif.

Synopsis—The SAFETY of the bactericide HEXACHLOROPHENE for use on the skin has been questioned in recent years. The authors have investigated primary IRRITATION, contact SENSITIZATION, PHOTOTOXICITY, and PHOTOSENSITIZATION with this chemical on animals. Results confirmed that hexachlorophene showed a higher degree of primary irritation than any other halogenated compound tested in this study. Irritation from this chemical increased with time and reached a peak 96 to 120 hours following application. Moreover, there was a difference in the irritant reaction to this chemical depending upon the solvents used.

In another study, photopatch tests of hexachlorophene were performed on guinea pigs and rabbits. A greater inflammatory reaction was observed at the irradiated site, as compared with the control site which had been treated topically with the chemical but without exposure to ultraviolet light. In addition, histological examination revealed disturbances of blood vessels apparently caused by topical application with hexachlorophene.

Introduction

Hexachlorophene (HCP) and other halogenated compounds active as bactericides have frequently been used in the preparation of deodorants and antiperspirants. Recently, it has been reported that bithionol and other compounds have the property of inducing a photoallergic reaction (1–10). As a result, emphasis has been placed on the necessity of appraising the safety of these bactericides for living organisms.

The safety of HCP for the skin was reviewed by Gump (11) in 1969. Reports on the occurrence of sensitization (12–14) and photosensitization

*Shiseido Laboratories, Yokohama, Japan.

(5, 8, 15–18) of HCP were presented. Generally speaking, however, it was concluded that HCP is a bactericide having a wide safety margin. HCP has been used extensively as a bactericide for over 20 years, without causing noticeable problems. This has been regarded as evidence that HCP is one of the safe bactericides.

The authors studied the safety of HCP for the skin mostly in experimental animals, by examining the capacity of this chemical to induce primary irritation, contact allergy, phototoxicity, and photoallergy.

Experimental Materials and Methods

Determination of Primary Irritation

Primary Irritation

Comparison of primary irritation between hexachlorophene and other halogenated compounds used as bactericides was done by an open patch test method on animals.

The animals used were male albino guinea pigs of the Hartley strain weighing 400–500 g and white male albino rabbits weighing 2,500–3,500 g. Hair on the back of the animal was cut with electric hair clippers. A depilatory* containing calcium thioglycolate was immediately applied to this area for depilation. Twenty-four hours after depilation, the following compounds, dissolved in acetone, were applied to the depilated area: hexachlorophene (0.01, 0.05, 0.1, 0.25, 0.5, 1, and 3%); 3,3′,4′,5-tetrachlorosalicylanide (TCSA) (0.1 0.25, 0.5, 1, and 3%); dichlorophene (DCP) [2,2′-methylenebis(4-chlorophenol)], 3,4′,5-tribromosalicylanilide (TBS), bithionol [2,2′-thiobis(4,6-dichlorophenol)], 3,4,4′-trichlorocarbanilide (TCC), and 3-trifluoromethyl-4,4′-dichlorocarbanilide (TFC) (0.5, 1, and 3%). Each chemical (0.03 ml) was applied to a circle on the back of the animals 1.5 cm in diameter. The sites of topical application were observed for the presence or absence of a skin reaction 24 and 48 hours after application. The intensity of skin reaction was graded in accordance with the criteria shown in Table I.

*Shiseido Hair Remover, Shiseido Company, Ltd., Tokyo, Japan.

Table I
Evaluation of Skin Reaction

No erythema	0
Very slight erythema	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema to slight eschar formation	4

Effect of Vehicles on Primary Irritation of Hexachlorophene in Man and Animals

HCP in such concentrations as indicated was dissolved in the following vehicles and applied topically to the backs of animals 24 hours after depilation: polyethylene glycol 400, 5 and 10%; olive oil, 0.25, 0.5, 1, and 3%; propylene glycol, 0.25, 0.5, and 1%; and acetone, 0.05, 0.1, 0.25, 0.5, and 1%. Each solution (0.03 ml) was applied topically to a circle 1.5 cm in diameter. Moreover, 0.03 g of petrolatum containing 0.25, 0.5, 1, and 3% of HCP was applied topically to an area 1.5 cm in diameter. The sites of application were observed for the presence or absence of a skin reaction and the intensity of the reaction was noted 24 and 48 hours after application. The intensity of skin reaction was graded as shown in Table I.

Closed Patch Test on Animals—HCP was dissolved in polyethylene glycol 400, olive oil, propylene glycol, and acetone. Hexachlorophene was also mixed with petrolatum in the concentrations indicated. Then 0.5 ml of each test solution or 0.5 g of petrolatum containing HCP was applied on a round piece of absorbent cloth 1.5 cm in diameter which had been attached to adhesive tape. This was used for the patch test. Adhesive tapes were applied immediately to the animal as a closed patch and kept in place for 24 hours. The sites of application of closed patches were observed for the presence or absence of a skin reaction, and the intensity of the reaction 24 and 48 hours after application was noted. The intensity of skin reaction was graded in accordance with the criteria shown in Table I.

Closed Patch Test on Humans—The volunteers were normal healthy human beings from 18 to 34 years of age and consisted of 25 males and 42 females. HCP solutions were prepared in different concentrations in the following vehicles: 0.1 and 0.3% in propylene glycol, 10% in olive oil, 10% in petrolatum, 10% in isopropyl myristate, and 10% in polyethylene glycol. Each test solution (0.05 ml) or 0.05 g of petrolatum containing HCP and petrolatum were applied on round pieces of absorbent cloth 1.5 cm in diameter held by adhesive tape for the patch test. These patches were applied to the surface of the forearm of each volunteer for the closed patch, and kept in place for 24 hours. The sites of application of the test materials were observed for the presence of a skin reaction and the intensity of the reaction 24 and 48 hours after application was noted. The intensity of the skin reaction was graded in accordance with the criteria shown in Table I.

Changes in Primary Irritant Reaction of Hexachlorophene on Animals with Time

The animals used were male albino guinea pigs of the Hartley strain weighing 400–500 g. Hair on the back of each animal was cut and depilated ac-

cording to the method previously indicated. Twenty-four hours after depilation, 0.03 ml of a 1% HCP solution in acetone was applied topically to each of four sites on the back of the guinea pig. Tissue specimens were taken by the skin punch biopsy method from the four sites of application after 1, 2, 3, and 4 days, respectively.

Each sample was fixed in 10% formalin solution, embedded in paraffin, and cut into sections 7μ in thickness. The sections were stained with hematoxylin and eosin and examined under a microscope at a magnification of 100 and 400 X.

Examination of Phototoxicity of HCP in Animals

The animals were those tested for primary irritation. A similar procedure was used to depilatate the skin. Twenty-four hours following depilation, two of the following concentrations such as 1, 0.5, 0.25, 0.1, 0.05, 0.01% of HCP dissolved in acetone were applied symmetrically on both sides, left and right, of the depilated area to circles 1.5 cm in diameter. Immediately after application, the area on one side was covered with aluminum foil. Thirty minutes later, the other side was irradiated with four fluorescent lamps* (for irradiation of ultraviolet rays at a wavelength of 300–400 mμ, with a peak at 360 mμ) which had been equipped with an ordinary glass filter to eliminate the wavelength within the range of sunburn. The distance from the light source to the skin was 10 cm. Irradiation was continued for 3 hours (1.12×10^8 ergs/cm^2). The test circles were observed for a reaction 24 and 48 hours after the end of irradiation. The intensity of skin reaction was graded in accordance with the criteria shown in Table I.

Examination of Contact Sensitization in Animals

Male albino guinea pigs of the Hartley strain weighing 400–500 g were used. The nuchal area of guinea pigs was shaved and dipilated as indicated previously. About 24 hours after depilation, 0.05 ml of 2% HCP solution in acetone was applied to a site about 2 x 2 cm in size in the nuchal area. This procedure was carried out daily for 5 consecutive days per week and repeated for 2 weeks.

Challenge was performed 2 weeks following the last topical application of the HCP solution. Hair on the back of a guinea pig was cut by the electric hair clipper and immediately depilatated. Twenty-four hours after depilation, 0.05 ml of 0.001, 0.01, 0.05, and 0.1% HCP solution in acetone was applied topically to sites 2 x 2 cm in size. The test sites were observed for the presence or absence of a skin reaction and the intensity of the reaction 24 and 48 hours after the procedure of challenge was recorded. The intensity of the skin reaction was graded in accordance with the criteria shown in Table I.

*Toshiba Model FL-20 BLB, 72 Horikawa-cho, Kawashi, Japan.

Examination of Photocontact Sensitization in Animals

The animals were the same as mentioned for contact sensitization. Twenty-four hours following depilation, 0.05 ml of 2% HCP solution in acetone was applied topically to a site about 2 x 2 cm in size on the nuchal area of the animal. About 30 minutes later, this site was exposed to ultraviolet rays. The light source used was composed of two Toshiba Model FL-20 BLB fluorescent lamps and two Model FL-20 SE fluorescent lamps (for irradiation of ultraviolet rays at a wavelength of 270–400 mμ) arranged alternately. The distance from the light source to the skin was 10 cm. The energy used was 1.18×10^8 ergs/cm^2. This procedure was carried out daily for 5 consecutive days per week and repeated for 2 weeks.

Challenge was performed 2 weeks after the last application of HCP solution. The same procedure as mentioned previously was applied to the skin for depilation. After 24 hours, 0.05 ml each of 0.001, 0.01, 0.05, and 0.1% HCP solution in acetone was applied topically to the sites arranged in two rows, as shown in Fig. 1. Immediately, the sites of one row were covered with aluminum foil to keep the light out. Thirty minutes after topical application, the sites in the other row were irradiated with four fluorescent lamps to which a glass filter was attached to eliminate sunburn. The distance from the light source to the skin was 10 cm. The energy used was 1.12×10^8 ergs/cm^2. The test sites were observed for the presence or absence of a skin reaction and the intensity of the reaction 24 and 48 hours after irradiation was recorded. The intensity of skin reaction was graded in accordance with the criteria shown in Table I.

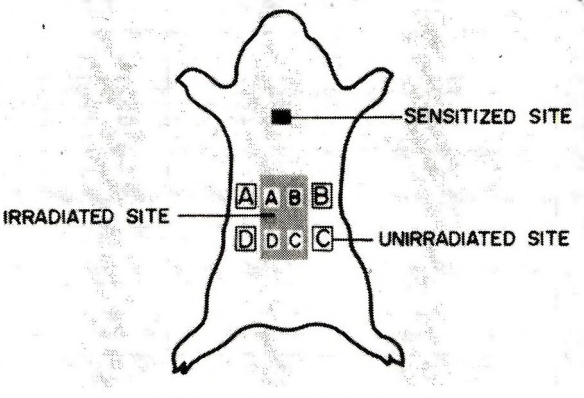

Figure 1. Challenge method

RESULTS

The comparison of primary irritation between hexachlorophene and other halogenated compounds used as bactericides by the open patch tests on animals is shown in Table II. Primary irritation was observed in guinea pigs

Table II
Primary Irritation of Halogenated Compounds in Acetone

Compound	Species[a]	Concentration (%)[b]						
		3.00	1.00	0.50	0.25	0.10	0.05	0.01
HCP	GP	10/10(1.8)	10/10(1.6)	10/10(1.4)	15/20(1.0)	6/20(1.0)	0/20	0/10
	R	5/5(1.8)	8/10(1.6)	8/10(1.9)	6/10(1.0)	3/10(1.3)	1/10(2.0)	0/10
DCP	GP	0/10	0/10	0/10				
	R	0/5	0/5	0/5				
TCSA	GP	10/10(1.0)	8/10(1.0)	4/10(1.0)	0/10	0/10		
	R	5/5(1.0)	3/5(1.0)	2/5(1.0)	0/5	0/5		
TBS	GP	0/10	0/10	0/10				
	R	0/5	0/5	0/5				
Bithionol	GP	0/10	0/10	0/10				
	R	0/5	0/5	0/5				
Fentichlor	GP	0/10	0/10	0/10				
	R	0/5	0/5	0/5				
TCC	GP	0/10	0/10	0/10				
	R	0/5	0/5	0/5				
TFC	GP	0/10	0/10	0/10				
	R	0/5	0/5	0/5				

[a]GP, guinea pig; R, rabbit.
[b]Figures in parentheses indicate intensity of reaction.

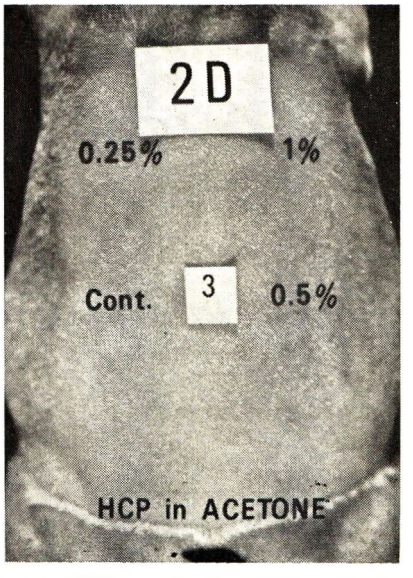

Figure 2. Primary irritation to HCP dissolved in acetone (marked erythematous reactions were shown with 0.5% an 1.0% HCP, and a slight erythema was shown with 0.25% HCP in the open patch test on guinea pigs)

applied with 0.1% or higher of HCP in acetone and in rabbits applied with 0.05% or higher concentration of HCP. A positive reaction expressed by a score of 1–2 was noticed in all the guinea pigs applied with 0.5% or higher concentration of HCP and in all the rabbits applied with 3% HCP. A positive reaction expressed by a score of 1–2 was recognized both in guinea pigs and rabbits applied with 0.5% or higher concentration of TCSA. Furthermore, when applied with 3% of TCSA, all the guinea pigs and rabbits presented such irritation as expressed by a score of 1–2. On the other hand, no primary irritation was observed at all in any animal applied with 3% of any of the other six halogenated compounds. Figure 2 shows the primary irritation to HCP dissolved in acetone.

The effects of vehicles upon the primary irritation of HCP in animals are shown in Tables III and IV. The skin irritation reaction was observed in guinea pigs applied with 5% and higher concentrations in polyethylene glycol 400, 0.5% and higher concentrations in olive oil, petrolatum, and propylene glycol, and 0.1% and higher concentrations in acetone. The results were the same in closed patch as in open patch tests. In the case of olive oil, however, the minimum concentration that produced irritation was 0.5% in the open and 1% in the closed patch tests.

The concentrations of HCP which produced irritation in all the experimental guinea pigs were 10% in polyethylene glycol 400, 3% in olive oil, 3% in petrolatum, and 1% in propylene glycol, regardless of the kind of patch test used. In the case of acetone, this concentration was 0.25% by the open or closed patch test. Skin irritation reaction was noticed in some of the rabbits tested with 5% in polyethylene glycol 400 vehicle (open patch test), 1% in olive oil, 0.5% in petrolatum, 0.5% (open patch test) and 0.25% (closed patch test) in propylene glycol, and 0.1% in acetone. The concentrations of HCP

Table III
Primary Irritation of HCP in Various Vehicles
(Guinea Pig)

Vehicle	Application	Concentration (%)[a]							
		10.00	5.00	3.00	1.00	0.50	0.25	0.10	0.05
Polyethylene glycol 400	Open	5/5(1.2)	2/10(1.0)	0/10					
	Closed	5/5(1.4)	3/10(1.0)	0/10					
Olive oil	Open			10/10(2.0)	3/10(1.3)	1/10(1.0)	0/10		
	Closed			10/10(2.0)	2/10(1.0)	0/10			
Petrolatum	Open			10/10(1.6)	6/10(1.1)	3/10(1.0)	0/10		
	Closed			10/10(1.6)	4/10(1.2)	1/10(1.0)	0/10		
Propylene glycol	Open				10/10(2.0)	10/10(1.6)	0/10		
	Closed				10/10(1.8)	8/10(1.5)	0/10		
Acetone	Open				7/7(1.8)	5/5(1.6)	5/5(1.4)	1/5(1.0)	0/5
	Closed				5/5(1.8)	5/5(1.4)	3/5(1.3)	1/5(1.0)	0/5

[a]Figures in parentheses indicate intensity of reaction.

Table IV
Primary Irritation of HCP in Various Vehicles
(Rabbit)

Vehicle	Application	Concentration (%)[a]							
		10.00	5.00	3.00	1.00	0.50	0.25	0.10	0.05
Polyethylene glycol 400	Open	1/5(1.0)	1/5(1.0)	0/5					
	Closed	0/5	0/5	0/5					
Olive oil	Open			5/5(1.8)	1/5(1.0)	0/5			
	Closed			5/5(1.8)	1/5(1.0)	0/5			
Petrolatum	Open			4/5(1.75)	4/5(1.5)	3/5(1.3)	0/5		
	Closed			4/5(1.5)	4/5(1.5)	2/5(1.5)	0/5		
Propylene glycol	Open				5/5(1.6)	2/5(1.0)	0/5		
	Closed				5/5(2.0)	5/5(1.8)	1/5(1.0)	0/5	
Acetone	Open				5/5(1.8)	5/5(1.6)	4/5(1.0)	2/5(1.0)	0/5
	Closed				5/5(1.8)	5/5(1.6)	4/5(1.25)	1/5(1.0)	0/5

[a]Figures in parentheses indicate intensity of reaction.

which produced irritation in all the experimental rabbits were 3% in olive oil, 1% (open patch test) and 0.5% (closed patch test) in propylene glycol, and 0.5% in acetone. In both guinea pigs and rabbits, the skin irritation reaction of HCP was most likely to occur when acetone was used as vehicle, and least likely to occur when polyethylene glycol 400 was used as vehicle. Petrolatum, olive oil, and propylene glycol were intermediate. There was little difference in results between the open and the closed patch test.

Table V and Fig. 3 show the primary irritation of hexachlorophene examined by closed patch test on human beings. It was not infrequent to see irritation from propylene glycol itself by the closed patch test. Therefore, it was regarded as positive when the reaction produced by the solution containing HCP was clearly stronger than that from propylene glycol alone serving as vehicle. When petrolatum, olive oil, isopropyl myristate, and polyethylene glycol 400 were used as vehicles, 10% HCP showed no irritation reaction at all in any subjects applied. On the other hand, when propylene glycol was used as the vehicle, a positive reaction was observed in 34 of 72 subjects applied with 0.3% of HCP and in 17 of 72 subjects applied with 0.1% of HCP. The authors observed an interesting pattern of irritation to HCP. One, 3, 5, and 10% HCP solutions in acetone were applied topically to sites on the back of 5 guinea pigs, and the sites were examined for the presence or absence of skin reaction and the intensity of the reaction for 2 weeks. A higher grade of positive reaction was noticed after 2 and 3 days rather than one day after the topical application, regardless of the concentration of HCP applied. Furthermore, when the average score of 5 guinea pigs was determined in accordance with the criteria shown in Table I, the reaction was increasingly intensified after the topical application and finally reached the highest level 4 to 5 days

Table V
Primary Irritation of HCP in Various Vehicles
(Closed Patch Test in Humans)

Vehicle	Concentration (%)	Subject[a]		
		Female	Male	Total
Propylene glycol	0.1	10/47(1.0)	7/25(1.0)	17/72(1.0)
Propylene glycol	0.3	25/47(1.32)	9/25(1.33)	34/72(1.32)
Petrolatum	10	0/47	0/25	0/72
Olive oil	10	0/47	0/25	0/72
Isopropyl myristate	10	0/47	0/25	0/72
Polyethylene glycol 400	10	0/47	0/25	0/72

[a]Figures in parentheses indicate intensity of reaction.

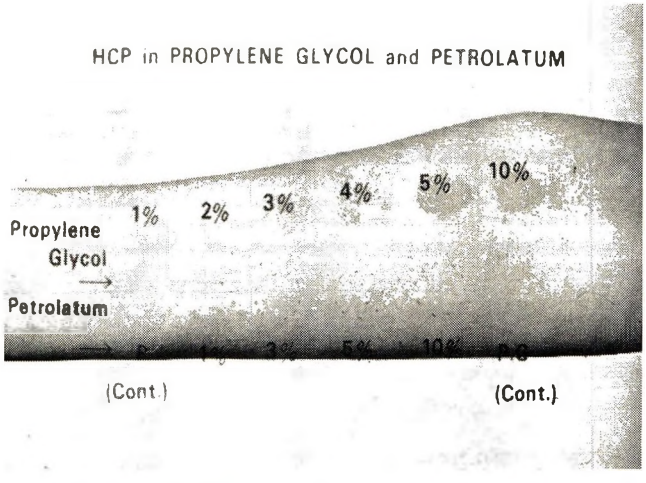

Figure 3. Primary irritation to HCP in propylene glycol and petrolatum on human subjects (marked erythema was found with 1% HCP in propylene glycol, but no inflammatory reaction was found with 10% HCP in petrolatum in the closed patch test for human skin)

after topical application. The intensity of the reaction then diminishes gradually as can be noted in Figs. 4 and 5.

The results of the histological examination of primary irritation of hexachlorophene on guinea pigs are shown in Fig. 6. Histological examination was carried out on animals administered topically with 1% HCP solution in acetone. Specimens were taken from these animals 1 to 4 days after topical application. The skin showed an almost normal histological picture 1 and 2 days

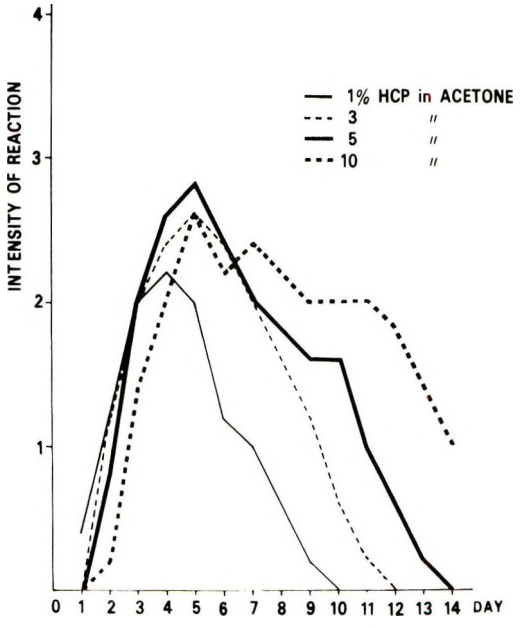

Figure 4. Development of primary irritant reaction (guinea pig)

after topical application. Three days after the application, extravascular outflow of erythrocytes was observed in the upper and middle layer of the dermis. In addition, degeneration of the walls of minute blood vessels was also noticed. On the other hand, the epidermis was almost normal. Cellular infiltration was not distinct in the dermis. Four days after the application, a marked cellular infiltration composed of small round cells, neutrophils, histiocytes, and a few eosinophils was observed in the upper and middle dermis. In addition, blood vessels were dilated and an extravasation of erythrocytes was noticed. Collagen fibers were considerably edematous. In the lower layer of the dermis, blood vessels were dilated and affected with thrombosis. Degeneration of vascular walls and extravascular outflow of erythrocytes were also noticed.

Figure 7 shows the results of examination of the animals for phototoxicity to HCP. In guinea pigs, the positive skin reaction was compared between the sites of HCP topical application alone and those of HCP topical application accompanied by ultraviolet irradiation. The results showed that positive skin reaction was always higher at the latter site, with HCP concentrations of 0.05, 0.1, 0.25, or 0.5% but not at 1%. In rabbits, the positive response was also greater at the irradiated site than at the nonirradiated site applied with 0.25% of HCP but the difference in response was less marked at 0.5 and 1.0% concentrations of HCP.

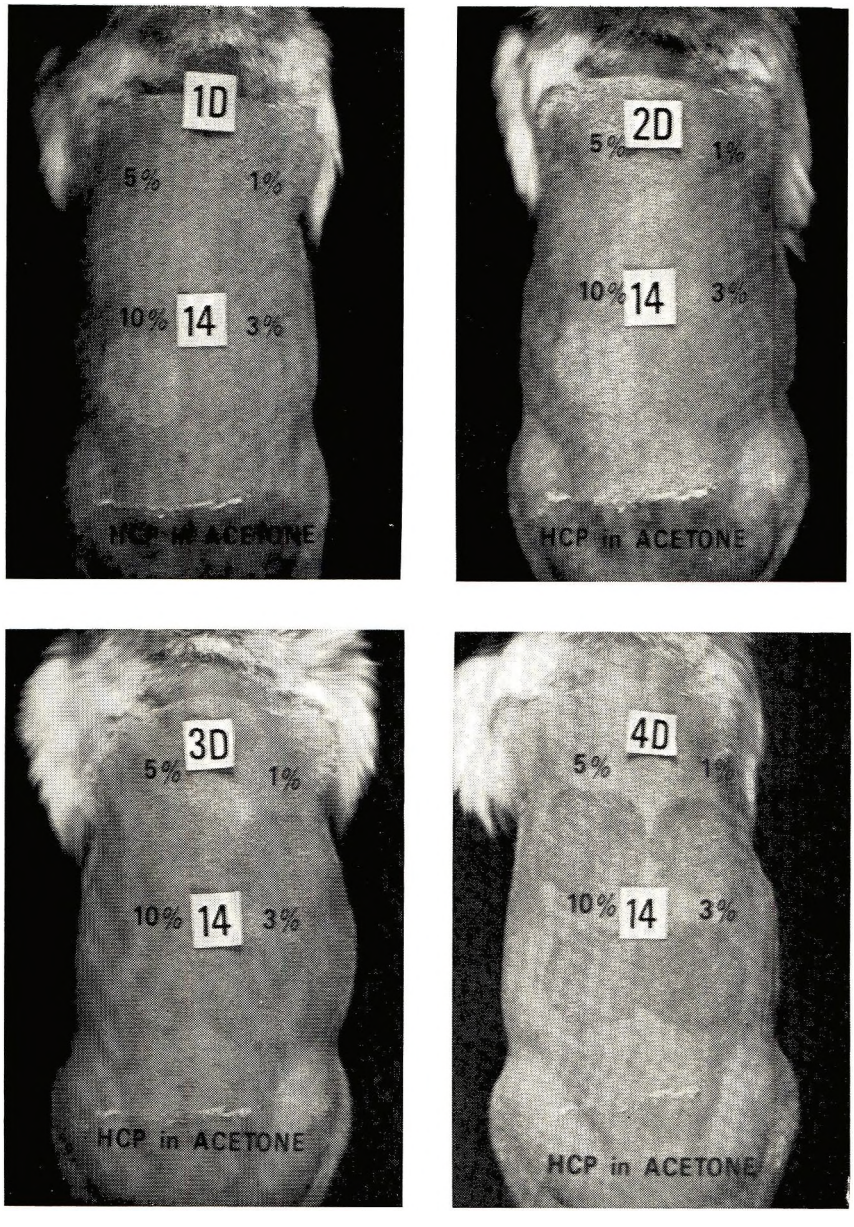

Figure 5. Change in intensity of primary irritant reactions to HCP 1, 2, 3, and 4 days after application

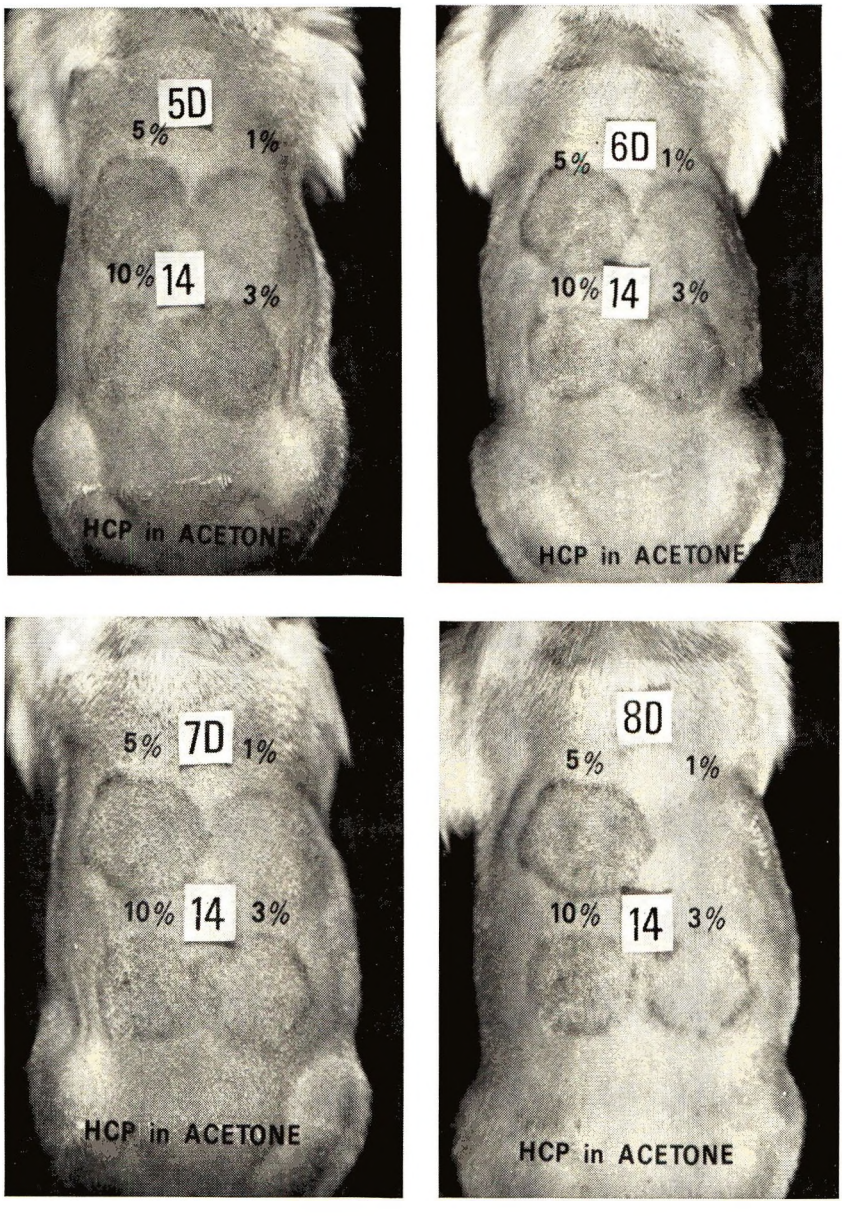

Figure 5 (continued). Change in intensity of primary irritant reactions to HCP 5, 6, 7, and 8 days after application

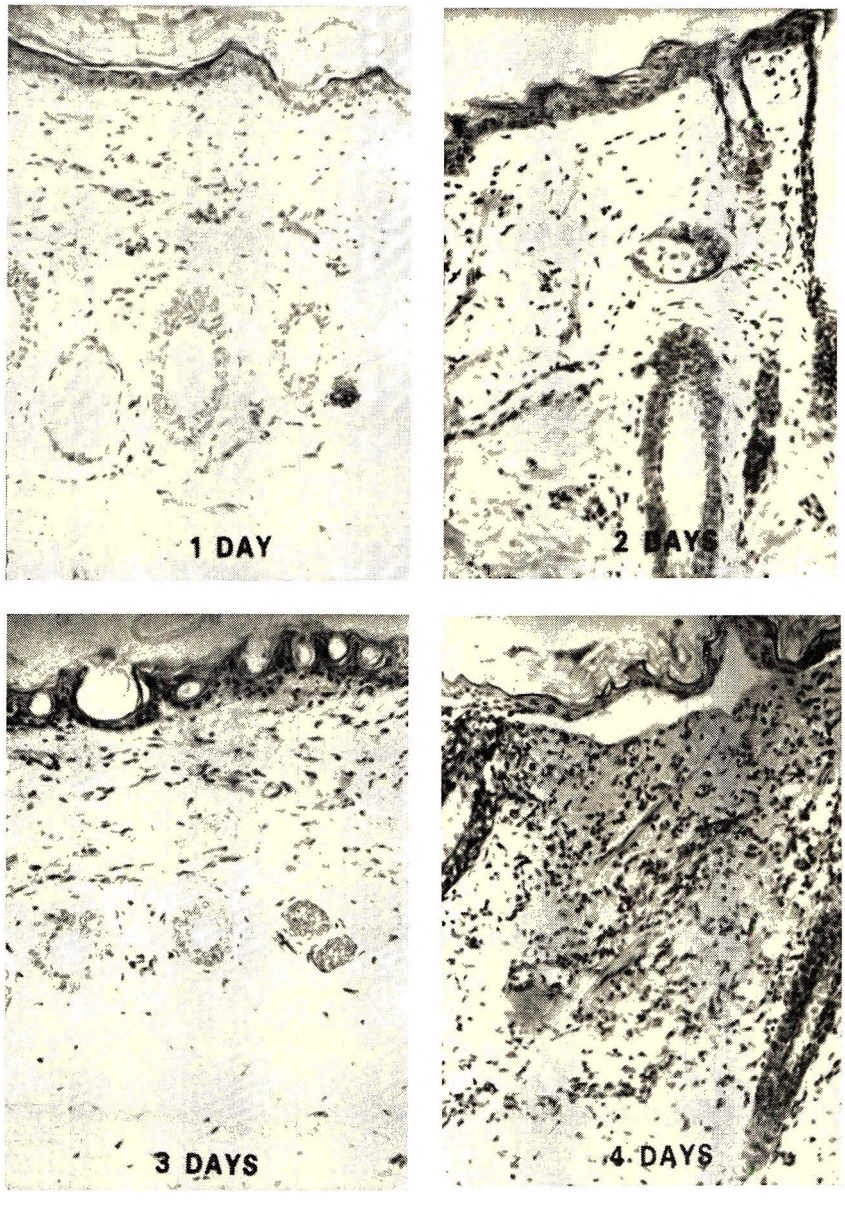

Figure 6. Histological findings of primary irritant reactions to HCP 1, 2, 3, and 4 days after application

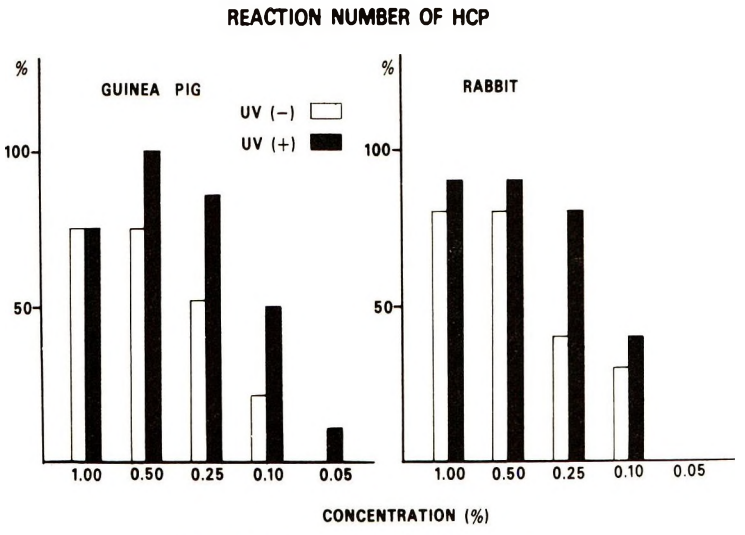

Figure 7. Phototoxity of HCP in acetone

Discussion

The authors examined HCP for safety to the skin by using experimental animals and man. HCP had a distinctly more potent primary irritancy potential upon animal skin than any other halogenated compound studied.

On the other hand, it was impossible to find any contact or photocontact sensitization with HCP. In 1969, Baker (19) reported 9 human cases with scrotal dermatitis and 1 case with buttock dermatitis caused by primary irritation with HCP. All cases were produced by a bath preparation containing HCP, except one which was caused by application of a skin cleanser containing this chemical. It is said that if a substance to which there is a low barrier resistance is applied continually, the mild irritant activity will have a cumulative effect, which gradually induces a fatigue phenomenon of the skin. Willis and Kligman (17) mentioned that HCP and other halogenated compounds remained in the cutaneous tissue for a considerably long time after having been in contact with the skin. Therefore, these points must be taken into full consideration when a preparation containing HCP is used continually.

Our experiments on animals and humans indicated that the primary irritant reaction of HCP is influenced markedly by the kind of vehicle used as seen in Table VI.

The irritant reaction of HCP was readily produced in guinea pigs and rabbits applied with this chemical dissolved in acetone. On the other hand, it was hardly induced in those animals administered with this chemical dissolved in polyethylene glycol 400. It was more easily induced in humans applied with

Table VI
Primary Irritant Threshold of HCP

Vehicle	Application	Subject		
		Guinea Pig	Rabbit	Human
Polyethylene glycol 400	Open	5%	5%	. . .
	Closed	5%	> 10%	> 10%
Olive oil	Open	0.5%	1.0%	. . .
	Closed	1.0%	1.0%	> 10%
Petrolatum	Open	0.5%	0.5%	. . .
	Closed	0.5%	0.5%	> 10%
Propylene glycol	Open	0.5%	0.5%	. . .
	Closed	0.5%	0.25%	0.1% <
Acetone	Open	0.1%	0.1%	. . .
	Closed	0.1%	0.1%	N.D.

HCP dissolved in propylene glycol as compared with HCP dissolved in PEG 400, olive oil, and petrolatum. No experiments were carried out on humans with HCP solution in acetone.

It has been reported that the reaction caused by a skin irritant is influenced considerably by the vehicle. This phenomenon was observed by Nilzen *et al.* (20) who reported that when acetone or ethanol was used as vehicle for DNCB, reactions to this chemical occurred about five times as often as when olive oil was used.

In Japan, Ishihara *et al.* (21) dissolved or suspended four kinds of surface active agents (1 anionic, 1 cationic, and 2 nonionic) in ethanol, isopropyl alcohol, water, and liquid paraffin and compared their skin irritant effects. They found a considerable variation in concentration of each agent producing irritant reactions, according to the relationship between the kind of agent and that of the vehicle. In general, the reaction occurred least readily when liquid paraffin had been used as the vehicle for each surface active agent. Therefore, it is important to examine the influence of vehicles to evaluate the skin irritation of a mild irritant substance.

In the authors' experiment, HCP incorporated in polyethylene glycol 400, olive oil, or petrolatum produced skin irritation in human beings less often than in guinea pigs or in rabbits. When HCP was dissolved in propylene glycol as the vehicle, the irritant reaction of HCP was induced in human beings at a lower concentration of HCP than in experimental animals. There was little difference in the minimal effective concentration of HCP required for the occurrence of irritant reaction between the guinea pig and the rabbit, regardless of the kind of vehicle used for HCP.

In addition, there was little difference between the open and the closed patch test, in the primary irritation of HCP, in the experimental animals regardless of the kind of vehicle. A reason for these results was presumed to be the lack of minor sudoriferous glands in these species.

The irritant reaction of HCP in animals was much higher in intensity 4 or 5 days than in 1 or 2 days after topical application. This result was obtained from animal experiments macroscopically and histologically. Microscopic examination of the specimen taken 3 days after the application revealed that the epidermis was hardly affected, but that erythrocytes showed an extravascular outflow and the vascular walls were degenerated. Although the cause of these specific reactions has not been clarified, the experimental result suggests that it may be necessary to observe the site of reaction for a considerably longer time after topical application of HCP.

Stott (22) presented the negative data for phototoxicity of HCP from his experiment on the ear of the guinea pig. In our experiment, the intensity of positive irritant reaction was always higher at the sites of HCP application followed by the irradiation than at the sites applied with HCP alone. However, the increase in intensity of irritant reaction to HCP influenced by the exposure of ultraviolet ray was remarkably low. Therefore, further examination for the presence or absence of phototoxicity of HCP should be performed before any conclusion is drawn on this problem.

Negative results of contact and photocontact sensitization of HCP in guinea pigs were obtained in our experiments. On the other hand, Harber *et al.* (18) obtained positive results from their experiment on 24 guinea pigs, observing 1 case of contact sensitization and 6 cases of photocontact sensitization.

Although a positive reaction was induced by the challenge with 0.1% of HCP in 4 of 20 sensitized animals and in 6 of 20 photosensitized animals in our experiments, it was finally judged that neither contact nor photocontact sensitization had taken place, since a primary irritant reaction could be induced by application with 0.1% HCP solution, and no positive reaction occurred when challenge had been made by a concentration of HCP not higher than 0.05%. In short, when such a substance as HCP which induces an irritant reaction at a low concentration is applied, it seems necessary to study the concentration of the substance used for challenge.

Summary

Hexachlorophene (HCP) had a more potent primary irritancy effect upon experimental animals than any other halogenated compound studied. The influence of vehicle for HCP was found to be significant in the primary irritant reaction to this chemical in experimental animals. The irritant reaction of HCP was more readily produced when acetone was used as vehicle than when polyethylene glycol 400 was used. A 50-fold difference in primary irritant threshold was noted between these two vehicles.

There was no difference in the primary irritant reaction of HCP in experimental animals between open and closed patch test. When examined by the closed patch test on human skin, a primary irritant reaction was produced by

HCP dissolved in propylene glycol at a lower concentration than HCP dissolved or suspended in any other vehicle tested.

The irritant reaction to HCP was compared between humans and experimental animals. When propylene glycol was used as vehicle for HCP, irritation was induced in human beings at a slightly lower concentration than in experimental animals. When any other vehicles were used, the irritant reaction to HCP was much more readily induced in experimental animals than in human beings.

The most intense primary irritant reaction to HCP was observed macroscopically in experimental animals 4 to 5 days after topical application. When histological examination was carried out on the site of primary irritant reaction to HCP in experimental animals, some disturbances of the vascular wall and extravasation of erythrocytes were observed.

Exposure to ultraviolet rays slightly intensified the primary irritant reactions of HCP. Neither contact sensitization nor photocontact sensitization of HCP was observed in any experimental animals.

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J. Soc. Cosmet. Chem., **25**, 131–138 (March 1974)

Oxidationsfarbstoffe: Bildungsmechanismen und Strukturen

HANS HUSEMEYER *

Vortrag anläßlich des VII. IFSCC-Kongresses in Hamburg vom 11. bis 15. September 1972

Synopsis — Oxidation Dyes: Mechanism of formation and structure. — The reaction of 1.4-DIAMINOBENZENE with derivatives of 1.3-DIAMINOBENZENE in AMMONIACAL AQUEOUS HYDROGEN PEROXIDE SOLUTIONS was investigated. The initially formed QUINONEDIIMINE COUPLES with other components to yield DYES OF THE TOLUYLENE BLUE TYPE which was discovered by O. N. Witt. The entire group of dyestuffs was synthesized by systematic changes of the substituents. Their spectral behavior and their RATE OF OXIDATION TO PHENAZINES at elevated temperature permit interesting insights into the positions of the MESOMERIC BASIC STATE.

In der Haarfärberei spielen die Oxidationsfarbstoffe eine besondere Rolle. Sie entstehen aus farblosen aromatischen Verbindungen im Haarschaft in Gegenwart von Ammoniak und Wasserstoffperoxid. Über ihren chemischen Aufbau existieren fast nur Vermutungen. Die einen ordnen sie den von O. N. Witt entdeckten Indaminen und Indophenolen zu, die anderen sprechen von hochmolekularen Substanzen vom Poly-Phenazin- bzw. Phenoxazintypus. Die außerordentliche Schwierigkeit, die sich bildenden Farbstoffe aus ammoniakalisch-wäßrigen, wasserstoffperoxidhaltigen Medien zu isolieren, hat bisher eine klare Entscheidung zwischen beiden Anschauungen verhindert. Hier auf einem Teilgebiet Klarheit zu schaffen, ist Zweck dieser Ausführungen.

Man betrachte folgende Reaktionspartner:

1. 1.4-Diaminobenzol (p-Phenylendiamin)
2. 1.3-Diaminobenzol (m-Phenylendiamin)
   1.3-Diamino-4-methylbenzol
   1.3-Diamino-4-methoxybenzol

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Das 1.4-Diaminobenzol reagiert im ammoniakalisch-wäßrigen Medium in Gegenwart von Wasserstoffperoxid mit den einzelnen Verbindungen der Gruppe 2 zu blauen Farbstoffen. Wie eingangs erwähnt, ist es unmöglich, die Farbstoffe in direktem Reaktionsgang zu isolieren, da sie einmal aufgrund der geringen Löslichkeit der Bildungskomponenten in Wasser nur in geringen Konzentrationen vorliegen, zum anderen mit Wasserstoffperoxid eine stöchiometrische Oxidation unmöglich ist. Es mußte somit ein anderer Weg beschritten werden. Wir entschlossen uns zunächst, ein Teilproblem anzugreifen: Die Wechselwirkung von 1.4-Diaminobenzol mit Oxidationsmitteln. Die Sichtung der Literatur führte uns auf die Arbeiten von Willstätter, Mayer und Pfannenstiel. Die genannten Autoren versuchten, aus dem 1.4-Diaminobenzol durch oxidative Dehydrierung das Chinondiimin herzustellen, und isolierten die gesuchte Verbindung in Form schwach gelblicher, analysenreiner Kristalle. Sie beschritten zwei Wege, die in *Abbildung 1* dargelegt sind:

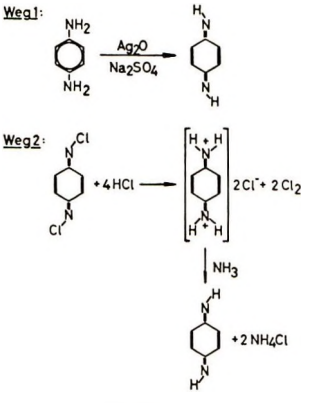


Abbildung 1

Weg 1 erfordert geringeren experimentellen Aufwand und wurde deshalb von uns zur Nacharbeitung ausgewählt. Es zeigte sich bald, daß bei diesem Verfahren die Darstellung von trockenem Silberoxid die Hauptschwierigkeit ist. Das frisch gefällte Silberoxid muß in einer absolut trockenen Atmosphäre zunächst mit Aceton, dann mit Äther von jeglichen Wasserspuren befreit werden, da das Chinondiimin, das bei der genannten Reaktion entsteht, äußerst hydrolyseempfindlich ist. Schüttelt man dann eine ätherische Lösung von 1.4-Diaminobenzol mit dem so präparierten Silberoxid in Kombination mit entwässertem Natriumsulfat, so entsteht eine schwach gelbliche ätherische Lösung des Chinondiimins, die für weitere Reaktionen Verwendung fand. Schon Willstätter hatte versucht, das Chinondiimin mit Dimethylanilin umzusetzen, und erhielt eine schwach gefärbte Lösung, die erst bei Wasser-

zusatz eine blaue Färbung annahm. Wir wiederholten diesen Versuch, verwendeten aber als Reaktionspartner das 1.3-Diaminobenzol. Es entstand eine in starker ätherischer Schicht tiefrote Lösung, die ebenfalls erst nach Zusatz von Wasser eine blaue Färbung annahm. In *Abbildung 2* sei das vermutete Reaktionsschema von Willstätter folgerichtig auf die hier behandelten Reaktionspartner übertragen:

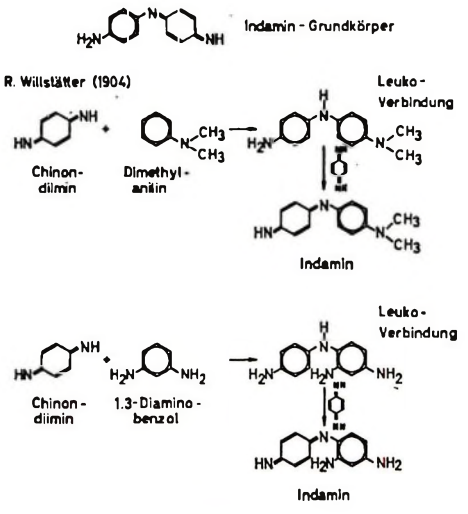


Abbildung 2

Das Chinondiimin kuppelt an der Stelle größter Elektronendichte mit dem Dimethylanilin bzw. dem 1.3-Diaminobenzol zur Leukoverbindung. Beim Dimethylanilin und dem 1.3-Diaminobenzol ist die Stelle größter Elektronendichte die 4-Stellung. Die Leukoverbindung wird von überschüssigem Chinondiimin aufgrund des Potentialgefälles zum Indoanilinfarbstoff dehydriert, das Chinondiimin geht bei diesem Prozeß in das 1.4-Diaminobenzol über.

Eine kritische Betrachtung der Formeln beider Indoanilinfarbstoffe zeigt, daß die Formulierung der chinoiden Struktur im Chinondiiminkern ein willkürlicher Akt ist. Eine verallgemeinerte Formulierung wird in *Abbildung 3* gezeigt.

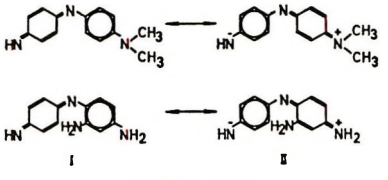


Abbildung 3

Die beiden aufgeführten Grenzformen der Indoanilinfarbstoffe stehen in einer Mesomeriebeziehung zueinander. Sie überlagern sich zum Grundzustand des Moleküls. Beide Kerne nehmen somit partiell an der chinoiden Struktur teil. Die Anteiligkeit wird durch die Wahl der Substituenten bestimmt, was eine besondere Rolle spielt.

Da es sich in beiden Fällen um nichtionische Farbstoffe handelt und somit auch kein ionogener Chromophor enthalten sein kann, bleibt die außergewöhnlich tiefe Farbigkeit der Verbindungen unerklärlich. Es bestanden deshalb erhebliche Zweifel an der Richtigkeit der Formulierung. Bei der Darstellung der Körper aus dem Chinondiimin und den Kupplungskomponenten hat es sich bereits gezeigt, daß die Farbstoffe nur in Gegenwart von Wasser eine blaue Farbe annehmen. Die enorme Farbänderung schließt einen Solvatochromie-Effekt aus. Die Farbstoffe müßten tiefergreifend in ihrer Struktur verändert worden sein. Unsere Hypothese zur Erklärung des Phänomens nahm die Verhaltensweise des Guanidins zum Muster *(Abbildung 4)*.

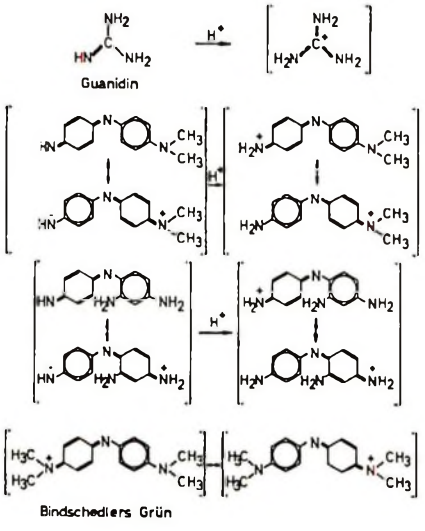


Abbildung 4

Während normalerweise, wie z. B. beim Anilin, die Basizität durch Mesomerie vermindert wird, wird in den aufgeführten Fällen die Basizität beträchtlich erhöht, da die Kationen durch die freiwerdende Mesomerie-Energie stabilisiert werden. Gesteigerter Valenzausgleich führt aber bei Farbstoffen zu einer bathochromen Verschiebung der Stelle maximaler Absorption im sichtbaren Bereich. Wenn diese Anschauung richtig ist, müssen die aufgeführten Farbstoffe dem Bindschedlerschen Grün als Grundkörper zugeordnet

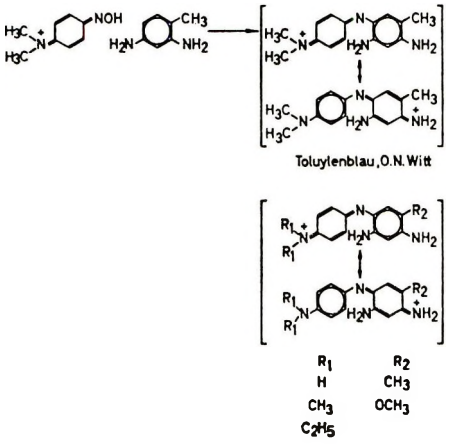
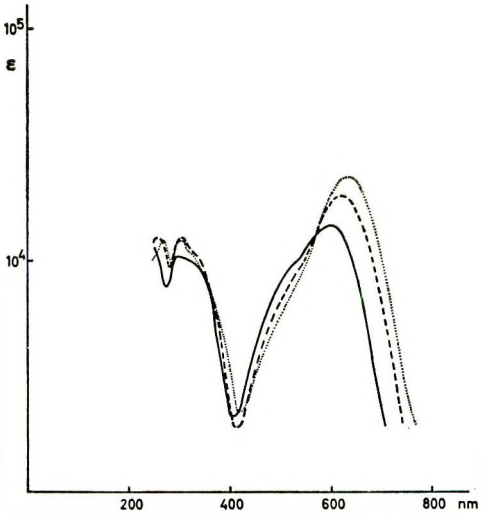


Abbildung 5

werden. Dies würde sowohl die Bandenintensität als auch die Bandenlage erklären. Ein Derivat von Bindschedlers Grün ist das von Witt entdeckte Toluylenblau. Er stellte es her durch Umsatz des salzsauren p-Nitrosodimethylanilins mit dem 1.3-Diamino-4-methylbenzol. Der Farbstoff fällt in

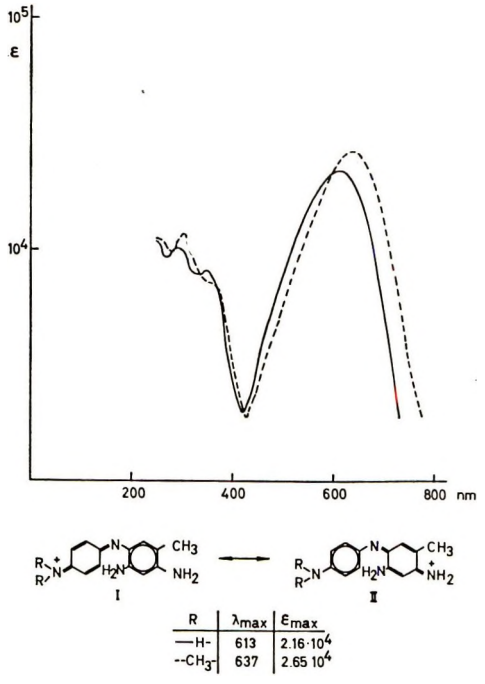


R	λ_{max}	ε_{max}
—H—	600	$1.43 \cdot 10^4$
—CH_3—	627	$1.97 \cdot 10^4$
—C_2H_5—	633	$2.37 \cdot 10^4$

Abbildung 6

schwarzgrünen Kristallen an und kann aus absolutem Äthanol durch Tieftemperatur-Umkristallisation gereinigt werden. Seine Struktur liegt eindeutig fest. Um die Anteiligkeit der beiden Benzolkerne des Farbstoffes an der chinoiden Struktur näher studieren zu können, stellten wir auf dem genannten Wege *(Abbildung 5)* Farbstoffe mit gleicher Grundstruktur, aber veränderten Substituenten her.

Die Reinheit der Farbstoffe wurde durch Dünnschicht-Chromatographie und Elementaranalyse ausgewiesen. Eine Zusammenstellung ihrer Spektren ist den *Abbildungen 6* und *7* zu entnehmen.



R	λmax	εmax
—H-	613	$2.16 \cdot 10^4$
--CH_3-	637	$2.65\ 10^4$

Abbildung 7

Vergleichen wir die Spektren in *Abbildung 6* und *7*, so ergeben sich folgende Gemeinsamkeiten:

Bei Abwandlung der Stickstoffsubstituenten vom Wasserstoff bis zur Äthylgruppe ist in allen Fällen eine Verschiebung der Stelle maximaler Lichtabsorption in Richtung größerer Wellenlängen festzustellen bei gleichzeitigem Anstieg der Extinktion. Dies hat seinen Grund in einem immer ausgeprägteren mesomeren Valenzausgleich zwischen den Strukturen I und II. Vergleichen wir die Einflüsse der Kernsubstituenten Methyl- und Methoxygruppe miteinander, so stellen wir beim Übergang von der Methyl- zur Methoxy-

gruppe eine hypsochrome Bandenverschiebung bei gleichzeitiger Depression der Extinktionen fest. Dies hat offensichtlich seinen Grund darin, daß die Struktur II im Grundzustand immer mehr überwiegt. Diese Anschauung kann durch folgendes Experiment erhärtet werden.

Löst man die Farbstoffe (Spektren in den *Abbildungen 6* und *7*) in einer Mischung aus Alkohol und Wasser 1 : 1 und erhitzt sie während einer Stunde auf 100° C, so zeigt das Dünnschicht-Chromatogramm die Bildung steigender Mengen Phenazin an, je längerwellig ein Farbstoff dieser Gruppe absorbiert. Diese Regel gilt bei dieser Farbstoffgruppe allgemein. Je anteiliger die mesomere Grenzstruktur I am Gesamtzustand ist, desto kleiner ist die Aktivierungsenergie der Addition der Aminogruppe an das chinoide Bindungssystem von I und desto größer ist die Geschwindigkeitskonstante dieser Reaktion. Sie wird im Folgenden noch einmal dargestellt *(Abbildung 8)*.

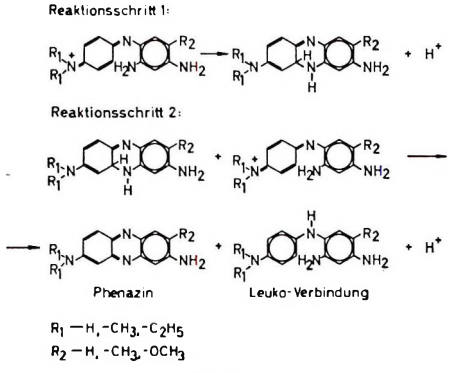


Abbildung 8

Ein Farbstoff der diskutierten Gruppe ist einer direkten Synthese in analysenreiner Form auf dem von Witt aufgezeigten Wege nicht zugänglich. Es gelingt nicht, das Reaktionsprodukt aus salzsaurem p-Nitrosoanilin mit 1.3-Diaminobenzol zu isolieren. Hier half folgender Kunstgriff weiter, der in Formeln wiedergegeben ist *(Abbildung 9)*.

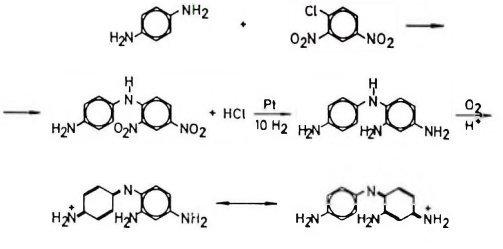


Abbildung 9

Setzt man das 1.4-Diaminobenzol mit 1-Chlor-2.4-dinitrobenzol um, so erhält man das 4-Amino-2′.4′-dinitrodiphenylamin. Diese Verbindung kann in absolutem Alkohol in Gegenwart von Platin aus Platinoxid (Adams) zur Leukoverbindung des gesuchten Farbstoffs reduziert werden. Anschließende Luftoxidation führt zu einer tiefblauen, optisch klaren Lösung, deren Spektrum nach Einstellung des Oxidationsgleichgewichtes aufgenommen wurde. Das Spektrum besitzt in allen wesentlichen Merkmalen äußerste Ähnlichkeit mit dem des Farbstoffes, der aus der Umsetzung von salzsaurem p-Nitrosoanilin und 1.3-Diamino-4-methylbenzol gewonnen wurde. Der nicht kernsubstituierte Farbstoff unterscheidet sich in der Bande maximaler Absorption nur um 2 nm in Richtung auf größere Wellenlängen, ansonsten verlaufen bei logarithmischer Auftragung der Absorptionskurven dieselben praktisch parallel. An einer analogen Struktur kann nicht gezweifelt werden.

Auch wurden die Chromatogramme der synthetisch dargestellten Farbstoffe mit denen der unter haarfärberischen Bedingungen hergestellten Farbstoffe sowohl einzeln als auch in Mischung miteinander verglichen. Es ergab sich volle Identität. Der Prozeß der Farbstoffbildung im Haar läßt sich wie folgt beschreiben:

Das 1.4-Diaminobenzol dringt in ammoniakalisch-wäßrigem Medium in das Haar ein, wird durch das Wasserstoffperoxid zum Chinondiimin dehydriert und kuppelt in Gegenwart von Derivaten des 1.3-Diaminobenzols zu Farbstoffen vom Toluylenblautypus. Die Farbstoffe sind ionogen und sterisch aufgrund der Molekülvergrößerung an das Keratin gebunden. Strukturen vom Polyphenazintypus konnten nicht nachgewiesen werden.

ZUSAMMENFASSUNG

Es wird die Reaktion von 1.4-Diaminobenzol mit Derivaten des 1.3-Diaminobenzols in wäßrig-ammoniakalischen, wasserstoffperoxidhaltigen Lösungen untersucht. Das primär gebildete Chinondiimin kuppelt mit den Komponenten zu Farbstoffen vom Typus des von O. N. Witt entdeckten Toluylenblaus. Durch systematischen Substituentenaustausch wurde die gesamte Farbstoffgruppe synthetisiert. Aus dem spektralen Verhalten und aus den Geschwindigkeitskonstanten ihrer Oxidation zu Phenazinen bei erhöhter Temperatur konnten interessante Einblicke in die Lage der Mesomerie-Grundzustände gewonnen werden.

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The Evaluation of Antiperspirant Efficacy—Influence of Certain Variables

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Presented May 4, 1973, Seminar, Cincinnati, Ohio

Synopsis—ANTIPERSPIRANT activity estimated by a GRAVIMETRIC PROCEDURE is discussed. The possible influence of several factors on observed EFFECTIVENESS are evaluated, namely, sweating rate, axilla treated, sweat collection conditions, and method of data analysis employed. Panelist-to-panelist variation in response is briefly discussed.

Introduction

Several systems have been employed by numerous investigators in evaluating antiperspirant activity. The simplest of these have been visual observation procedures (1–3). They are of value as screening procedures in which several potential antiperspirant agents can be simultaneously evaluated on the same panelists. A second type of evaluation is that which provides precise measurements of sweat output from limited areas of skin. The procedures of James (4) and Jenkins *et al.* (5) are two somewhat different examples of this basic method. Evaluations of this type provide precise measurements of sweat output; however, the complexity of the method renders it impractical for evaluations on the relatively large number of panelists which are required to establish a fairly accurate estimation of antiperspirant activity in a representative population cross-section.

In addition, we have observed in limited attempts to evaluate collections made from small areas of the axilla a very critical requirement that repeated collections be always made from exactly the same area. The repositioning of collection units on exactly the same test area for each collection is difficult to control within the minimal variation which is permissible.

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The third type is based on gravimetric determinations of sweat output over relatively long time intervals. Procedures of this type are as a rule based on the procedure of Fredell and Read (6) and Daley (7). The procedure of this type reported by Wooding (8) presents in some detail the procedure we employ.

In our procedure the panelists are required to abstain from the use of all antiperspirant materials for at last one week prior to initiation of the study and throughout the study if it is a cross-over design. The sweat collections are carried out in controlled temperature rooms, 100 ±2°F and at about 35% relative humidity. Sweat collections are made during two successive 20-min periods using tared Webril®* pads. These collections are preceded by a 40-min conditioning period in the hot room during which the panelists hold unweighed Webril pads in their axillae. In early attempts to carry out evaluations by this procedure, attempts were made to utilize data obtained during the periods immediately following the panelists' entry into the hot room. Extreme variations in sweating patterns of the panelists were encountered during the first 20-min period. Values were somewhat more reproducible during the period 20–40 min following the panelists' entry into the hot room; however, excessive variations in sweating patterns were still observed in some panelists. In essentially all hot room studies we have carried out during the past 10 years, sweat collections have been restricted to the period 40–80 min following panelists' entry into the hot room. We will present data which show that sweat collection data obtained during two successive 20-min collection periods, 40–60 and 60–80 minutes after hot room entry, are adequately reproducible to provide the basis for precise evaluation of antiperspirant activity. For convenience of reference, these collections will be referred to as Collections B and C.

Data Evaluation Methods

There is disagreement between investigators as to the evaluation procedure which should be applied to data obtained by various procedures. Our experiences indicate that the most consistent characteristic of individual sweating patterns is the ratio of sweat output by the two axillae of each individual. We have assembled sweating data from individual panelists in a series of several randomly selected studies. These studies varied from studies covering 10 days to some which encompassed 16 calendar weeks. Studies which cover longer time intervals are of multiple cross-over types. In these cases a 2-week recovery period always elapsed between test weeks.

The accuracy of estimations of antiperspirant activity can be no more accurate than accuracy and reproducibility of data from the panelists utilized in the study.

*Kendall Co., Walpole, Mass.

Table I

Data from Panelists in a Recent Study Showing Individual Control Sweat Collections, Sweating Ratios, Mean Values, and Per Cent Coefficient of Variations

Panelist		Collections									% Coeff.
		1/8/73		1/10/73		1/12/73		1/15/73			of
No.	Axilla	B	C	B	C	B	C	B	C	Mean	Var.
1	R (T), mg	547	808	613	735	606	1020[a]	510[a]	730	696	22
	L (C), mg	319	493	433	530	435	704	433	561	488	22
	Ratio	1.714	1.638	1.415	1.386	1.393	1.448	1.177	1.301	1.434	11
2	R (T), mg	606	514	92[b]	330	469	710[a]	269[a]	567	489	28
	L (C), mg	544	463	116	377	408	616	216	375	424	27
	Ratio	1.113	1.110	0.793	0.875	1.149	1.152	1.245	1.512	1.163	14
3	R (T), mg	1027	1143	927	1085	1310[a]	1247	840[a]	1095	1084	13
	L (C), mg	1180	1282	1057	1127	1353	1357	968	1199	1190	11
	Ratio	0.870	0.891	0.877	0.962	0.968	0.918	0.867	0.913	0.908	3.4
4	R (T), mg	376	408	380	295	511[a]	491	263[a]	372	387	21
	L (C), mg	454	363	491	388	522	500	302	401	428	17
	Ratio	0.828	1.123	0.773	0.760	0.978	0.982	0.870	0.927	0.905	12
5	L (T), mg	748[a]	1254	1087	1042	1411[a]	927	938	810	1027	20
	R (C), mg	681	1111	895	829	1350	737	776	606	873	26
	Ratio	1.098	1.128	1.214	1.256	1.045	1.257	1.208	1.336	1.192	8.3
6	R (T), mg	958[a]	260[a]	432	819	685	352	499	581	573	39
	L (C), mg	1726	488	696	1391	1038	574	836	1059	976	40
	Ratio	0.555	0.532	0.620	0.588	0.659	0.613	0.596	0.548	0.588	9.1
7	L (T), mg	536	479	552	501	594[a]	540	407[a]	439	506	11
	R (C), mg	569	519	548	622	637	620	398	520	554	13
	Ratio	0.942	0.922	1.007	0.805	0.932	0.870	1.022	0.844	0.918	7.6
								Mean (T)		680	22
								Mean (C)		705	22
								Mean Ratio		1.015	9.3

[a] Extremes in collections for each panelist.

[b] Data not used due to marked variation from other values and collections below 100 mg.

Data presented in Table I show control sweat collections from a portion of the data from a typical study. This table also shows mean values for sweat collections from each axilla of individual panelists and individual and mean sweating ratios for each panelist. Coefficients of variation of each of these means are also shown. This table is presented so the data presented in Table II can be more readily evaluated.

In Table II are presented mean control values from a series of tests which were derived as shown in Table I. Data presented in Table II very clearly indicate that sweating ratios of individual panelists are much more reproducible and are much less subject to day-to-day variations than are individual measurements of sweat output from individual axillae. These ratios are also

Table II

Mean Control Sweat Collections from Test (T) Axilla and Control (C) Axilla (Mean Sweating Ratios and Mean Coefficient of Variations for 8 Recent Tests)

Study	No. of Panelists	No. of Collections	Time Spread of Detns (Weeks)	Axilla T(mg)	Coef. of Var. (%)	C(mg)	Coef. of Var. (%)	Ratio T/C	Coef. of Var. (%)
A	24	16	10	434	43	451	42	0.991	15
B	12	8	4	433	24	429	25	1.001	11
C	12	8	4	573	27	622	25	0.958	12
D	12	12	7	584	26	604	25	0.999	11
E	12	12	7	567	26	577	25	0.991	12
F	24	8	10	536	30	568	32	0.972	17
G	12	28	19	542	29	633	26	0.850	18
H	12	28	19	618	31	593	33	1.020	17
Mean				523	31	552	30	0.974	15

virtually independent of day-to-day variations in sweating rates observed in individual panelists. This is demonstrated in Table I, which indicates extremes in sweat collections for each panelist and their corresponding sweating ratios.

As reported by other investigators, e.g., Wooding (8), sweat output from the right axilla is slightly higher than from the left axilla. The distribution of panelists showing right-over-left ratios from 0.500 to 1.750 at 0.100 increments is shown in Fig. 1 for right-handed and left-handed individuals. The mean ratio for each group and the mean of all panelists determined from weighted values to compensate for the differences in numbers of right- and left-handed individuals are shown.

Results of analysis of these randomly selected data indicate that there is a correlation between right-left sweating rates of panelists and whether they are right-handed or left-handed. As many of us have assumed, the dominant armpit produces slightly greater perspiration. There are many reversals in both groups and the mean R/L ratios of the two groups are not statistically different.

In all cases, except where noted in the following discussions, per cent reductions in sweating were evaluated by determining the shift in sweating ratios. The mean control sweating ratios were determined in a minimum of eight collections distributed over at least four control days. The post-treatment sweating ratios were adjusted to compensate for the deviation of individual mean control ratios from 1.000. The basic formula for these calculations is:

$$\left(1.000 - \frac{\text{post-treatment ratio}}{\text{mean control ratio}}\right) 100 = \% \text{ reduction in sweating}$$

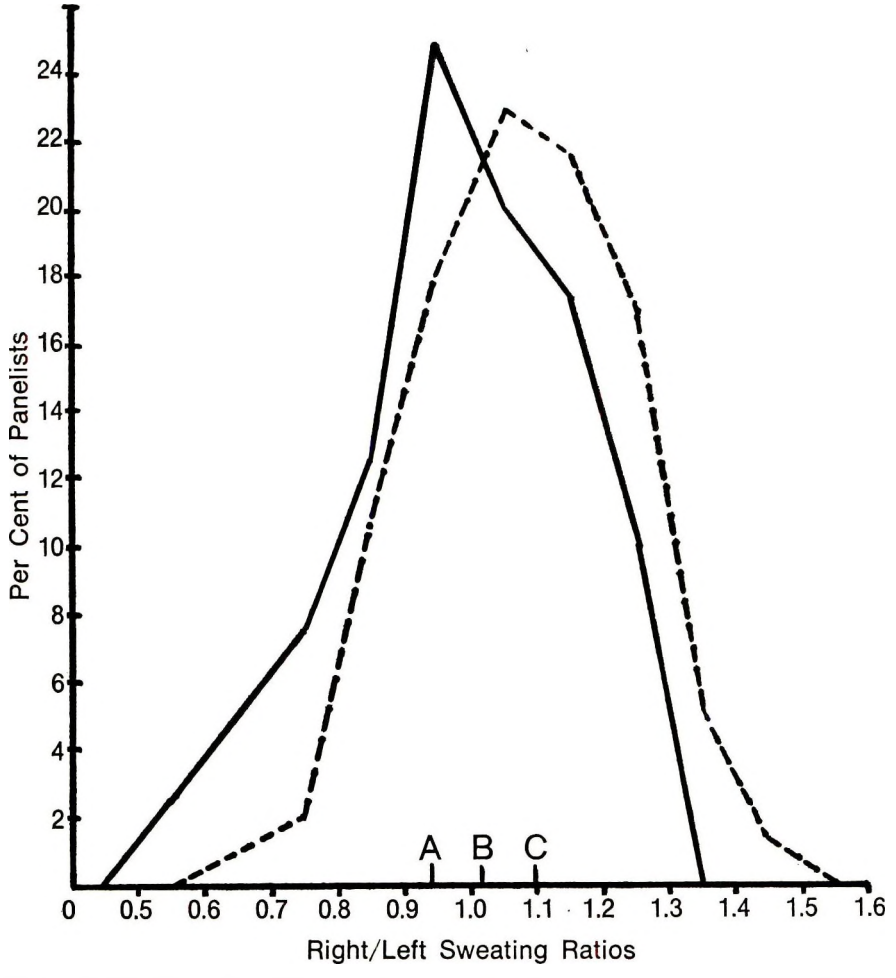

Figure 1. Distribution of R/L sweating ratios of right-handed and left-handed individuals
——— Left-handed panelists
- - - - Right-handed panelists
A. Mean left-handed
B. Mean left- and right-handed
C. Mean right-handed

Ratios are always calculated by dividing milligrams of sweat collected from test (treated or to-be-treated) (T) axilla by that collected from the control (untreated) (C) axilla. This procedure provides an estimation of per cent reduction. Data will be presented which indicate that the values obtained are very similar to those determined by direct comparisons between milligrams of sweat collected from treated and untreated axillae.

In order to illustrate the sensitivity of a procedure dependent on the utilization of shifts in sweating ratios to evaluate reductions in sweating ratios,

Table III

Unadjusted and Adjusted Control Sweating Ratios

Collection No.	Panelist No. 1	2	3	4	5	6	7	8	9	10	11	12
Unadjusted												
1B	1.272	0.953	0.913	0.717	0.927	0.602	1.230	1.053	1.028	0.836	0.688	1.169
1C	1.541	1.111	0.916	0.862	0.991	0.722	1.005	0.961	0.941	0.801	0.723	1.072
2B	1.271	1.203	0.746	0.831	1.098	0.730	1.051	1.238	1.094	0.705	0.692	1.245
2C	1.440	1.358	0.887	0.816	1.121	0.801	1.013	1.171	1.014	0.710	0.625	1.348
3B	1.297	0.852	0.775	0.625	1.074	0.921	1.313	1.191	0.931	0.895	0.645	1.183
3C	1.412	0.901	0.896	0.665	1.168	0.817	0.947	1.116	0.931	0.792	0.540	1.249
4B	1.421	0.946	1.070	0.598	1.018	0.727	0.990	0.966	1.305	0.860	0.756	1.369
4C	1.381	1.053	0.986	0.580	1.051	0.834	0.853	0.936	1.090	0.727	0.687	1.312
Mean	1.379	1.047	0.898	0.711	1.056	0.769	1.050	1.079	1.041	0.790	0.669	1.243
Adjusted												
1B	0.922	0.910	1.017	1.008	0.878	0.783	1.171	0.976	0.988	1.058	1.028	0.940
1C	1.117	1.061	1.020	1.212	0.938	0.939	0.957	0.891	0.904	1.014	1.081	0.862
2B	0.922	1.149	0.831	1.169	1.040	0.949	1.001	1.147	1.051	0.892	1.034	1.002
2C	1.044	1.297	0.988	1.148	1.062	1.042	0.965	1.085	0.974	0.899	0.934	1.084
3B	0.941	0.814	0.863	0.879	1.017	1.198	1.250	1.104	0.894	1.133	0.964	0.952
3C	1.024	0.861	0.998	0.935	1.106	1.062	0.902	1.034	0.894	1.003	0.807	1.005
4B	1.030	0.904	1.192	0.841	0.964	0.945	0.943	0.895	1.254	1.089	1.130	1.101
4C	1.001	1.006	1.098	0.816	0.995	1.085	0.812	0.867	1.047	0.920	1.027	1.056
Mean	1.000	1.000	1.001	1.001	1.000	1.000	1.000	1.000	1.001	1.001	1.001	1.000
Std. dev.	0.063	0.152	0.109	0.147	0.067	0.117	0.134	0.101	0.113	0.084	0.093	0.075
Std. error	0.022	0.054	0.039	0.052	0.024	0.041	0.047	0.036	0.040	0.030	0.033	0.027
Mean					1.000							
Standard error of mean of all values					0.011							

Table III shows a set of control sweating ratios which was taken from a randomly selected study. This table presents 8 individual control sweating ratios from each of 12 panelists, the mean control sweating ratios, and the individual control sweating ratios following adjustment by dividing them by the individual panelists' mean control ratios. The mean adjusted control ratio by this procedure will always be 1.000, but the standard deviations of individual ratios adjusted to a uniform base of 1.000 will vary. The group mean and the standard error of the mean of the adjusted control ratios are shown. These values are used in calculating the sweat reduction values and their confidence limits in actual evaluations of antiperspirant activity. Since evaluations are based on individual post-treatment days, the standard error for each post-treatment day should be taken as a truer estimation of test sensitivity—approximately ±5% at the 95% confidence level. This represents data from only 12 panelists. With larger panels the sensitivity is considerably greater.

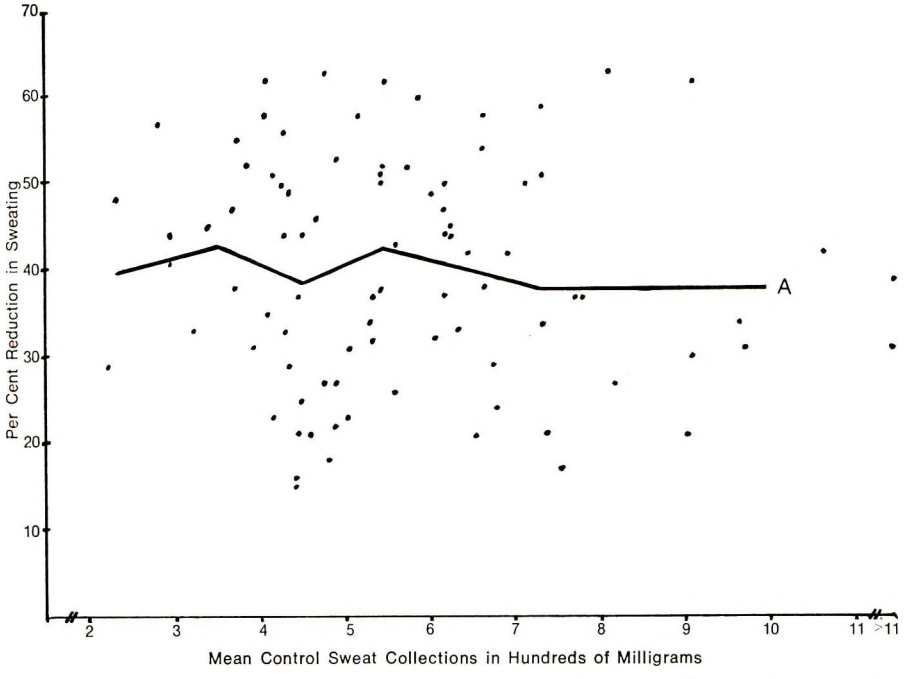

Figure 2. Per cent reduction in sweating *vs.* mean control sweat collections for individual panelists
A. Mean 39.0% reduction

Factors Influencing Effectiveness

Sweating Rates

The effects of several factors which may influence the apparent efficacy of antiperspirants were evaluated. The first factor investigated was the influence of perspiration rate on product effectiveness. For these evaluations data from 89 panelists are presented in Fig. 2, as a scatter chart showing reductions in sweating *versus* the sweat collections from the untreated axillae. These data are from four recently completed tests in which the mean sweat reductions were about 39%. These tests were randomly selected, the only criteria being that the mean reductions for each of the four tests were between 38% and 41%. It is obvious from this chart that there is no apparent correlation between sweating rate and reductions in sweating observed.

A distribution curve was prepared from the data used in preparation of Fig. 2. Data from eleven panelists from one additional study on 10% aluminum chlorohydrol were added to provide a total of 100 panelists. The materials evaluated on these panelists were either aqueous 10% aluminum chlorohydrol or highly effective marketed aerosol products. This curve is shown in

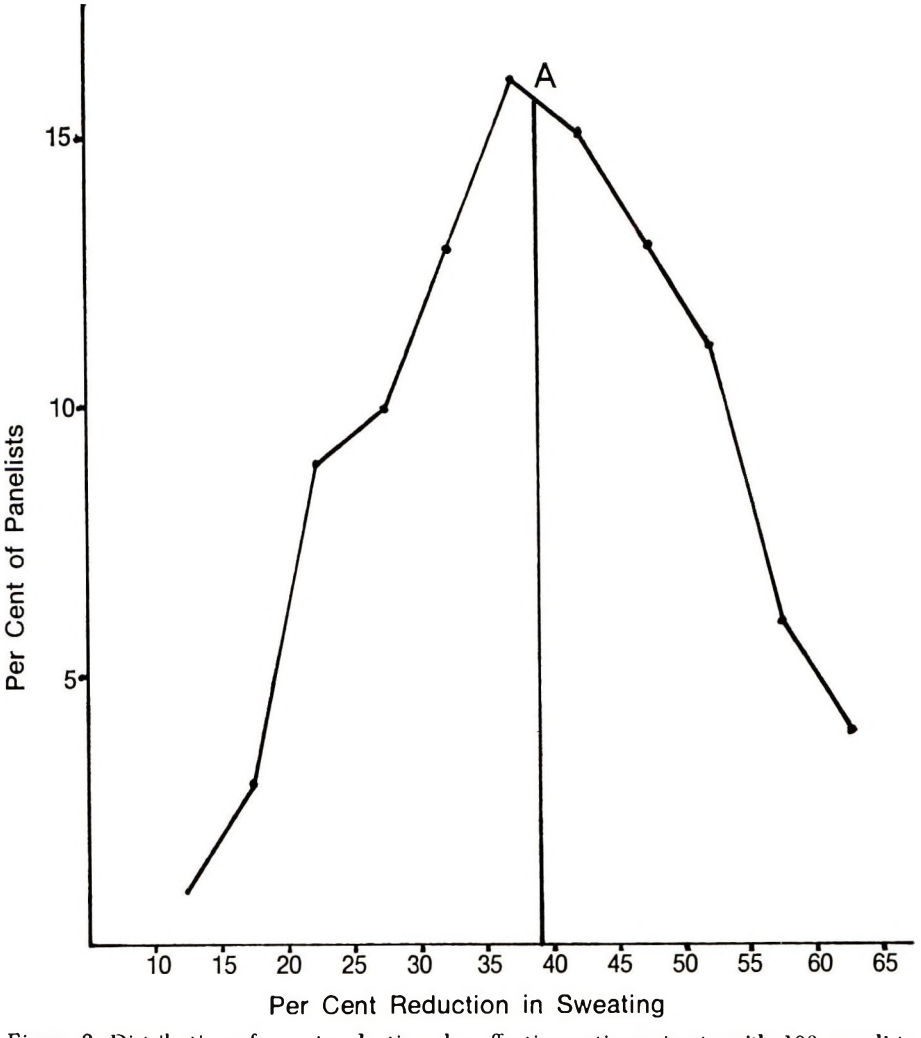

Figure 3. Distribution of sweat reductions by effective antiperspirants with 100 panelists
A. Mean 39.0% reduction

Fig. 3. The per cent reductions in sweating between 10% and 65% were plotted at 5% increments. This curve indicates that the responses of the panelists to effective antiperspirants follow an essentially normal distribution.

There are many factors which influence antiperspirant activity. A minor variation in formula composition is one of the most critical and is one which is occasionally not recognized. A formula additive may seriously inhibit antiperspirant activity, or in certain instances may definitely enhance activity. Additives which reduce formula irritancy without adversely affecting antiperspirant activity are in this last class.

There is marked panelist-to-panelist variation in responses to many factors. We have had the occasion to observe some samples, such as unformulated aluminum chloride, which reduce sweating of some panelists by 40–50% and increase sweating of other panelists by a similar amount. Panelists showing marked increases in sweating (properspirant activity) will usually show visual axillary irritation. However, we have observed many instances in which samples which are effective on most panelists exhibit no antiperspirant effect—or even properspirant activity—on some panelists and there is no visual evidence of axillary irritation. This would indicate that there is some factor other than inactivation of antiperspirant activity by formula components which results in certain panelists' specificity of decreased individual efficacy. This is discussed more specifically later in this presentation.

Sweat Collection Temperature

Several studies have been carried out in which antiperspirant activity was determined from sweat collections made in the 100°F room and under ambient conditions on successive days. The ambient collections were made during 3-hour periods during which the sweat collection pads were held in the axillae by means of commercially available dress shields. Results from three such studies are summarized in Table IV.

Table IV

Comparison of Activity at 100°F and Ambient Temperature
(Results Shown as Per Cent Reductions)

Study	Test Material	No. of Panelists	Collection Conditions	
			100°F	Ambient
1	Commercial Roll-on	20	32.2 ± 6.9	32.5 ± 9.6
2	Aerosol Powder A	24	23.0 ± 4.4	26.0 ± 5.0
2	Aerosol Powder B	24	8.0 ± 3.2	9.0 ± 5.3
3	Aerosol Powder A	12	25.5 ± 8.1	21.0 ± 9.2
3	Aerosol Powder B	12	27.4 ± 7.0	26.6 ± 11.0

Method of Data Analysis

There are several commonly applied procedures for estimating antiperspirant activity. Data from four studies were evaluated by three different procedures. The same data were used in each of these three evaluations. In all studies the test materials were applied to one axilla of each panelist following a series of control collections prior to sample application. The outline shown in Table V will facilitate description of the evaluations.

The per cent reduction values and 95% confidence limits as determined by each procedure are listed in Table VI. Procedure A is subject to greatest

Table V

Derivation of Various Methods of Data Analysis[a]

	Control Collections					Post-Treatment Collections				
Axilla	1	2	3	4	Mean	1[b]	2	3	4	Mean
R (T)	CT	CT	CT	CT	CT_M	PTT	PTT	PTT	PTT	PTT_M
L (C)	CU	CU	CU	CU	CU_M	PTU	PTU	PTU	PTU	PTU_M
Ratio	R	R	R	R	R_M	R	R	R	R	
Adjusted ratio						AR	AR	AR	AR	AR_M

Procedure		
A	$100 - (PTT_M \div CT_M \times 100)$	= % reduction
B	$100 - (PTT_M \div PTU_M \times 100)$	= % reduction
C	$100 - (AR \times 100)$	= % reduction

[a] Symbol Identification.

C = control collection; T = treated axilla

PT = post-treatment collection; U = untreated control axilla

R = unadjusted ratio; M subscript = mean values used in calculations

AR = adjusted post-treatment ratio, $\frac{\text{post-treatment ratio}}{\text{mean control ratio}}$

[b] First post-treatment collections were made following two applications.

Table VI

Comparative Results (Per Cent Reductions) Obtained in Three Methods of Analysis

	Procedure		
Test	A	B	C
1	24.6 ± 13.2	33.7 ± 3.7	30.7 ± 3.7
2	29.9 ± 7.8	23.0 ± 5.1	21.5 ± 4.8
3	60.6 ± 8.0	55.6 ± 5.2	56.2 ± 3.1
4	4.1 ± 10.4	6.1 ± 7.4	8.2 ± 5.4

variation as evaluations are dependent on day-to-day variations in sweat rate of the individuals. Procedures B and C should yield comparable results provided the mean right-to-left sweating ratios of the panelists approach 1.000. Due to marked day-to-day variations in sweat output from the same axilla, tests carried out by Procedure A may indicate significant properspirant effects on one day and marked sweat reductions on the following day.

A modification of Procedure C has proven to be particularly valuable in demonstrating significant differences of samples of similar efficacy. In this modification the normal control sweating ratios are determined as above. Both axillae are treated and shifts in the adjusted post-treatment ratios are determined. All ratios—controls and post-treatment—are made by assigning axillary treatment designations to correspond in a uniform manner, such as

with Samples A and B to T and U, as shown in the above format, so ratios are calculated A/B for all panelists during control and post-treatment periods. While this procedure is very sensitive in showing differences in antiperspirant activity, which is its primary purpose, estimations of reductions of both samples can be also made by applying Procedure A to the data.

Procedure Reproducibility and Panelist Variability

In compiling data which demonstrate the reproducibility of the outlined procedures, we frequently include a 10% w/w aqueous solution of aluminum chlorohydrol as a reference sample in cross-over studies. These evaluations have always been based on observed shifts in sweating ratios.

Values from six 12-panelist studies for this reference are shown in Table VII. These were carried out as cross-over studies with formulated aerosol or lotion antiperspirants. The reference sample was applied by swabbing 0.5-ml aliquots over the designated axillae in Tests 1, 3, and 6, and by applying a 2-sec spray from a Preval®* aerosol unit in Tests 2, 4, and 5.

Table VII

Comparison of Values (Per Cent Reductions) 1 and 2 Hours Following Sample Application

		No. of Applications	
		3	4
		Post-Treatment Interval	
Test No.	Panelists	1 hour	2 hours
1	12	49.0 ± 10.0	47.0 ± 8.6
2	11	43.0 ± 7.0	41.0 ± 6.4
3	12	43.0 ± 6.8	37.0 ± 8.1
4	12	33.3 ± 10.0	31.3 ± 11.5
5	12	46.4 ± 7.6	. . .
6	12	37.3 ± 7.2	32.9 ± 10.0

The variations in reductions in sweating observed in these six studies, 33.3% to 49.0%, are due to the comparative responsiveness of the panelists to applications of aluminum chlorohydrol. This panelist-to-panelist variation is a problem we have not been able to overcome, but can be partially compensated for by carrying out evaluations on larger panels of 30 or more. This will overcome the variability to a large extent.

It has been suggested that we exclude panelists who do not show a significant reduction in sweating. Our experiences indicate that this is not advisable. Failure of panelists to show reductions in sweating is not uniform for all test materials, particularly formulated samples.

*Manufactured by Precision Valve Corp., Yonkers, N.Y.

Table VIII

Per Cent Reductions in a Single Study on Four Market Products

Panelist No.	Sample A	B	C	D
1	40	52	53	46
2	20	0	0	18
3	29	11	12	29
4	10	7	16	0
5	17	3	0	0
6	10	0	4	0
7	30	25	32	59
8	31	20	37	5
9	28	43	52	43
10	6	41	23	23
11	21	41	38	49
12	18	5	13	37
13	6	42	42	34
14	0	0	0	28
15	0	34	53	59
16	0	13	18	40
17	15	47	42	23
18	27	28	19	16
19	16	12	12	0
20	12	40	46	9
21	2	22	19	6
22	15	34	51	16
23	1	42	37	48
24	20	28	26	47
Mean	15.6 ± 4.5	24.6 ± 6.4	26.9 ± 7.2	26.5 ± 7.8

Table VIII shows per cent reductions resulting from the application of four market products to 24 panelists. These data are from a recent four-way cross-over study. The panelists employed in this study included an unusually high per cent of individuals who did not respond to active antiperspirant formulations. A more typical panel of this size would contain one or two such resistant panelists. Samples B and C in this table are very similar and we have evaluated them in many studies. The values obtained in most such studies have shown 35–40% reduction in sweating. Sample D in this study is a formulation type which frequently produces axillary irritation. Sample A is a type intermediate between B or C and D.

Due to the extreme variation in values obtained in this study, an attempt was made to determine if a correlation could be demonstrated between irritation and failure to achieve antiperspirant activity. We determined that Samples B and C were essentially nonirritating when applied under occlusive patches to the panelists in this study. Sample D was found to be moderately irritating to about 50% of the panelists and Sample A was irritating to about

25% of the panelists. Distinct correlation between irritancy and poor efficacy was not demonstrated, however. That is, some individuals who showed irritation also showed marked reductions in sweating, and others who showed little or no antiperspirant effect did not show irritation from the patch applications.

The fact that seven of these panelists (Nos. 1, 3, 7, 9, 11, 18, and 24) show similar responses to all four products, and six others (Nos. 8, 10, 13, 15, 19, and 23) show similar responses to three of the four samples indicates that all samples are properly formulated to achieve expected efficacy. The variations in responses observed in the remaining 12 panelists are apparently due to specific individual differences. It is particularly inadvisable to exclude panelists on the basis of failure to show antiperspirant activity if the developed formulation is for use in substantiating claims for specific reductions in sweating. By the use of selected panelists we could achieve mean sweat reduction values twice that obtained from a nonselected random population. Panelists are excluded who fail to consistently yield at least 100 mg of sweat from each axilla during control collections. These are less than 1% of the panelists enrolled. The only other basis for exclusion is the lack of reasonable uniformity in control sweat collection ratios. These probably represent individuals who will not abide by standard precautions which are necessary in order to obtain reproducible values and very few such panelists are encountered. Most panelists can be readily indoctrinated in the proper regimen.

We have occasionally heard the comment that the outlined procedures are not accurate since submitted samples do not show a dose response curve. We have demonstrated in several studies, most of which were carried out early in the development of our procedure about 15 years ago, that typical dose responses are obtained with active aluminum salts. However, a plateau of maximum reductions is reached at concentrations considerably below concentrations present in essentially all typical market products.

Recently, we carried out comparative studies on 7% and 10% aqueous solutions of aluminum chlorohydrol. In this study the mean reductions in sweating determined on 24 panelists one hour after 2, 3, and 4 once-daily applications were 26% from the 7% solution and 45% from the 10% solution. In a similar recent study on 10% and 20% aluminum chlorohydrol solutions, the value for the 10% solution was 42% and 39% for the 20% solution. Unfortunately, we do not have data on sufficient intermediate concentrations to accurately plot a concentration response curve.

During the past three months we have been accumulating data from panelist questionnaires from which we hoped to be able to arrive at an estimation of practical significance of reductions in sweating determined in controlled laboratory studies. Our goals were to answer two questions: Is there a correlation between milligrams of sweat collected and panelist complaints of sweating during normal daily activities, and at what level of laboratory demonstrated reduction in sweating is there a noticeable difference in axillary

sweating of the panelists during their daily activities? We have accumulated reams of questionnaires, but little usable data, since most of the panelists did not report noticeable sweating during their daily activity. We intend to continue this data accumulation during the forthcoming summer. The limited responses of noticed differences in axillary sweating have shown, in general, less sweating from treated axillae. The data accumulated are not sufficient to comprise a valid statistical analysis. It is contemplated that when a sufficient compilation of data is achieved it will be presented in an additional article.

Summary

Portions of data accumulated during the past year in the course of numerous antiperspirant efficacy studies were presented. It was demonstrated that:

1. Reductions in sweating are independent of the sweating rate of the panelists.
2. Sweat output from the two axillae is slightly higher from the dominant hand axilla.
3. The response of panelists to antiperspirant activity of effective products follows an essentially normal curve distribution.
4. Evaluations made at 100°F are about the same as those made during ambient conditions.
5. The axillary sweating ratios are much more uniform than are sweating rates when sweat collections are made repeatedly from the same panelist.
6. Sweat reductions are essentially the same when calculations are based on sweating rates and shifts in sweating ratios. Confidence limits of values based on ratios are much narrower than those based on sweating rates.
7. Marked variations are shown in the panelist-to-panelist response to application of antiperspirant formulations; these variations are not uniform from one formulation to another.

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The Commission of Sin through the Medium of the Skin Patch Test

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Presented May 4, 1973, Seminar, Cincinnati, Ohio

Synopsis—The SKIN PATCH TEST is a valuable instrument. In the hands of well-meaning, but misguided, individuals the power of this instrument is creating significant PROBLEMS for MEDICINE in general and for the COSMETIC INDUSTRY in particular.

Introduction

In 1900, Jadassohn introduced the concept of the skin patch test (1). In the interim an extensive evolutionary process has produced many variations in technic and scope. A thread of relationship exists among these diverse test procedures; occasionally it is obliterated completely. All are performed upon normal or altered skin with the intent of measuring the degree of reactivity of this organ to a test substance offered under a contrived environmental state.

The intent of this report is neither to catalogue these many tests nor to dwell on the inestimable contribution each has made to research, medicine, and industry. Instead, the focus of attention will be placed on modes of operation in which the patch test may occasionally be the direct or supportive mechanism for disseminating unnecessary confusion in the laboratory, the clinician's office, as well as the market place; confusion which may occur innocently enough, and can be avoided. The cosmetic industry is significantly affected by skin patch-test conduct, and therefore a discussion of this subject is opportune.

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Modes of Operation

Example I

Well-intentioned authors writing in reputable medical journals publish articles with all-inclusive titles linking allergic contact type dermatitis to a consumer product, not necessarily from a single manufacturer, such as a powder puff, nail base-coat, eye glass, and perfume. A vivid description of the eruption is linked to product usage and then conclusively proven by a lesser or greater collection of sophisticated positive patch test data.

The effect of this approach in the current climate of consumerism and controls is enormous. Immediately, the reader dermatologist acquires a new mini-syndrome and the nation's lay science writers uncover an exciting threat to society to reveal in their syndicated columns. Even the Wall Street Journal runs an item on it.

The author of one such report discovered 9 cases in a single year from an "average" practice in close proximity to a metropolitan area. In his hurried study 19 separate products in the class were involved. Let us accept the skin test data as unimpeachable and assume this author's experience reflects what is happening in a practice population of approximately 100,000.

Extrapolating these figures to the general population by any of several technics, we should expect 18,000 to 27,000 professionally recognized complaints annually to this class of consumer product.

In an informal poll of 12 dermatologists with American Board certification associated with a major metropolitan teaching center—men and women whose practices reflect experience from a population greater than 1,000,000—the yield of suspected cases of dermatitis attributable to the consumer product in question did not reach 9 for the entire group in the more than 2 years since the original article was published.

Why this wide discrepancy, particularly with consumer sales of this product category increasing annually?

Example II

We are a society of collectors from antique automobiles to zithers. We search for the rare and dream of the unobtainable. Each time the stamp collector approaches the Postal Service window to purchase the latest commemoratives he relives the fantasy of being handed a sheet of stamps with the airplane upside down. Some of my dermatologic colleagues achieve this exhilaration through publication of the medical curiosity (in this instance the first documented report of an allergic contact dermatitis to substance X) confirmed by positive skin patch test.

There is no quarrel with the need for cataloguing such information. Perhaps the North American or International Contact Dermatitis Research Groups should be the repository. Why, however, is a trivial tidbit of knowl-

edge afforded the same status and prominence in dermatologic literature as a major advance in medical and scientific knowledge?

Example III

Allergy is an acquired state of reactivity. It is manifested when specifically sensitized tissue—the shock organ—is exposed to the allergen in question. A dose relationship exists. It is particularly characteristic for the allergic mechanism to be activated by unusually minute amounts of the allergen. Although the foregoing statements are an oversimplification of the subject, they are basic tenets in the technic of skin patch testing. Deviation from these principles demands cautious interpretation of the test results.

We are presently observing skin patch test technics that bear little or no relationship to customary usage of a consumer product (e.g., 10 times and 20 times use concentration of a suspected allergen, incorporation of irritating agents in the test vehicle, especially devised vehicles with unusual keratin or epidermal penetrating characteristics, and preliminary stripping of keratin). The test results from such procedures may complicate and confuse what they purport to simplify and the neomycin story illustrates it best.

Current tabulations of common agents causing allergic contact type dermatitis position neomycin high on the roster. This questionable honor was belatedly acquired because the conventional closed skin patch test with use-concentration of neomycin failed to produce positive tests in selected patients in whom the association was suspected. However, when the test concentration was increased by a factor of 10 or 20 times use, the harvest of positive results improved. Patients whose biologic mechanism persisted in being sluggish, however, were then stimulated, or whipped, into conformity by a hypodermic intradermal injection of neomycin. Furthermore, the dermatologic literature cautions the observer not to be impatient in his search for positive skin tests. He is advised that delayed reactions are common. If early readings are negative, look again; the reward will appear in 5 or 7 days. Since it takes about 5–7 days to "incubate" an allergic state where none existed before, one should not really be surprised by the efficiency of this skin patch test technic, which is, unfortunately, the established procedure for demonstrating neomycin allergy.

A startling piece of research in 1967 by Raab (2,3) revealed that neomycin shared a particularly basic chemical characteristic with a few other substances, e.g., polymyxin B and compound 48/80. Raab showed that neomycin is capable of degranulating mast cells which provoke the release of histamine. Raab recognized that neomycin must have an allergy-producing potential similar to many other substances; however, it is neomycin's mast cell depleting properties that are exceptional and have gone unrecognized. Skin testing with high concentrations or by intradermal injections of neomycin may elicit neomycin's particular irritant qualities, qualities that are not being separated from an allergic response (4).

A recent study by Schorr *et al.* (5) emphasizes reproducibility of test results and convincingly separates neomycin reactors from nonreactors. However, regretably, it does not establish the nature of the process or processes that are responsible for the dermal reactivity. Within the patient population, neomycin dermatoses, as well as the skin tests for establishing them, may be the result of histamine release due to a chemical irritation rather than an allergic phenomenon.

A noteworthy report which helps to purge neomycin of its onus considers the vehicle in which neomycin is presented to skin, suggesting that penetrability through the epidermis is an important factor. Hjorth (6) in his 1968 review of neomycin reactors at the Finsen Institute emphasized: "In proportion to their sale creams, lotions and powders containing neomycin were rarely connected with sensitization. This investigation suggests that neomycin ointments are the major cause of sensitization to this antibiotic."

How thorough is the neomycin overkill? Four years after publication of Raab's and Hjorth's reports a regulatory agency proposed to deny further certification of selected neomycin consumer products based on a literature review that did not include the work of either.

Example IV

A few years ago a dermatologist was shocked by the remark that the diagnosis of hair-dye dermatitis in his patient due to an allergy to *p*-phenylenediamine (PPD) was circumstantial at best and could scientifically be false; furthermore, his admonition that the patient never dye her hair again may be needlessly condemning her for life to a hair color she finds most obnoxious.

The case he presented was straightforward enough: a woman of 38 years was unhappy with her prematurely greying brown-black hair. It made her look and feel 10 years older. She was convinced it was creating domestic problems. For 2 years, on a regular 8–10 week schedule, she had dyed her hair to its normal uniform color with great success and personal satisfaction. Twenty-four hours prior to each application a carefully executed skin patch test as described by the manufacturer had been performed and found to be negative. However, the morning after the last hair coloring procedure, which was carried out in every detail as to technic and product, exactly as those which preceded it, the patient awoke with redness, itching, roughness, and swelling about the ears and hair line with accentuation over forehead and upper eyelids.

When the patient presented herself and her story to the same dermatologist several hours later, the eruption had grown more severe. A tentative diagnosis of hair-dye dermatitis was made; immediate treatment with topical and oral corticosteroids was instituted. Recovery was prompt and complete. A month later, as scheduled, the patient returned for a diagnostic 48-hour

closed skin patch test with fresh 2% PPD in petrolatum, the recognized standard concentration and vehicle. Upon removal of the patch a one to two-plus reaction was observed; twenty-four hours later the test site was clearly confirmed as a strong one-plus reaction. A contralateral control site with petrolatum alone was negative In the intervening month between treatment and test, information was received from the manufacturer that the hair coloring product in question was of the "permanent" or oxidation type and contained PPD and related dye intermediates in its formulation.

Despite the clinical and laboratory evidence in this patient, the final diagnosis of allergic eczematous contact type dermatitis due to PPD could be and was wrong. The admonition against further exposure to hair coloring products was unnecessary. A. A. Fisher and this author have studied a number of PPD patch test–positive individuals who tolerate repeated and routine exposure to PPD-containing hair coloring products without adverse reactions. (7,8). Such individuals demonstrate a one-plus or slightly greater reaction to the 48-hour closed skin patch test with 2% PPD in petrolatum. The manufacturer's recommended open 24-hour skin test with the product is usually negative in such subjects. This open type product-use-skin test is more practical as a screening procedure than previously realized.

Any number of common household products, allergens as well as primary irritants–from hair spray to oven cleaner–used the evening before the appearance of the eruption could have accounted for the patient's presenting dermatitis.

The presence of an allergic state proven by skin patch test does not necessarily reflect a subject's threshold of response under actual conditions of exposure to the consumer product. Dose relationship under contrived test conditions are not the same as dose relationships under use conditions.

Summary

The foregoing are a few examples of many. They are offered as representative of the ongoing confusion to which the scientific, medical, and industrial communities should direct their attention. The skin patch test is a valuable means to an end. Rigid discipline is required to avoid reversal of this equation. A beguilingly simple procedure provokes an extremely complex biologic mechanism subject to all the vagaries that can be associated with the response of living tissue. It behooves the practitioner to be humble in his interpretation.

Perhaps the cause-and-effect relationship seemingly confirmed by skin patch test data may be mere coincidence. Does it stand the test of time? Is the relationship reproducible by others? A local or a temporary situation or the zeal of an investigator are worthy of consideration. Established scientific publications might act more critically toward disseminating valuable contributions. Newsletters would be a better means for expressing personal experi-

ences or to test the validity of inadequately ripened concepts. Scientists representing industry have been known to cooperate with physicians in the critical preparation of a scientific publication. More of such mutual respect and understanding must be cultivated. All will benefit thereby.

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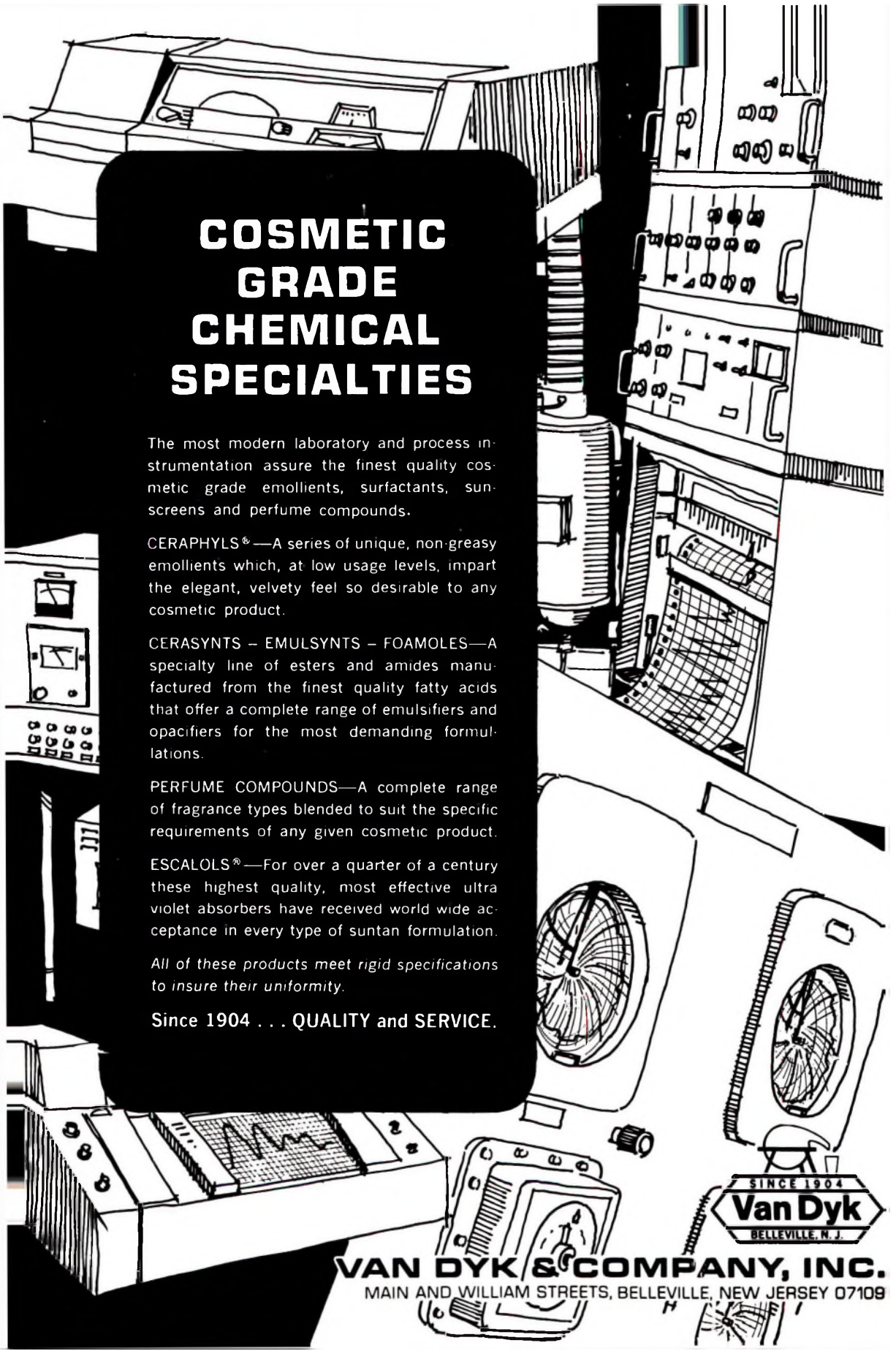

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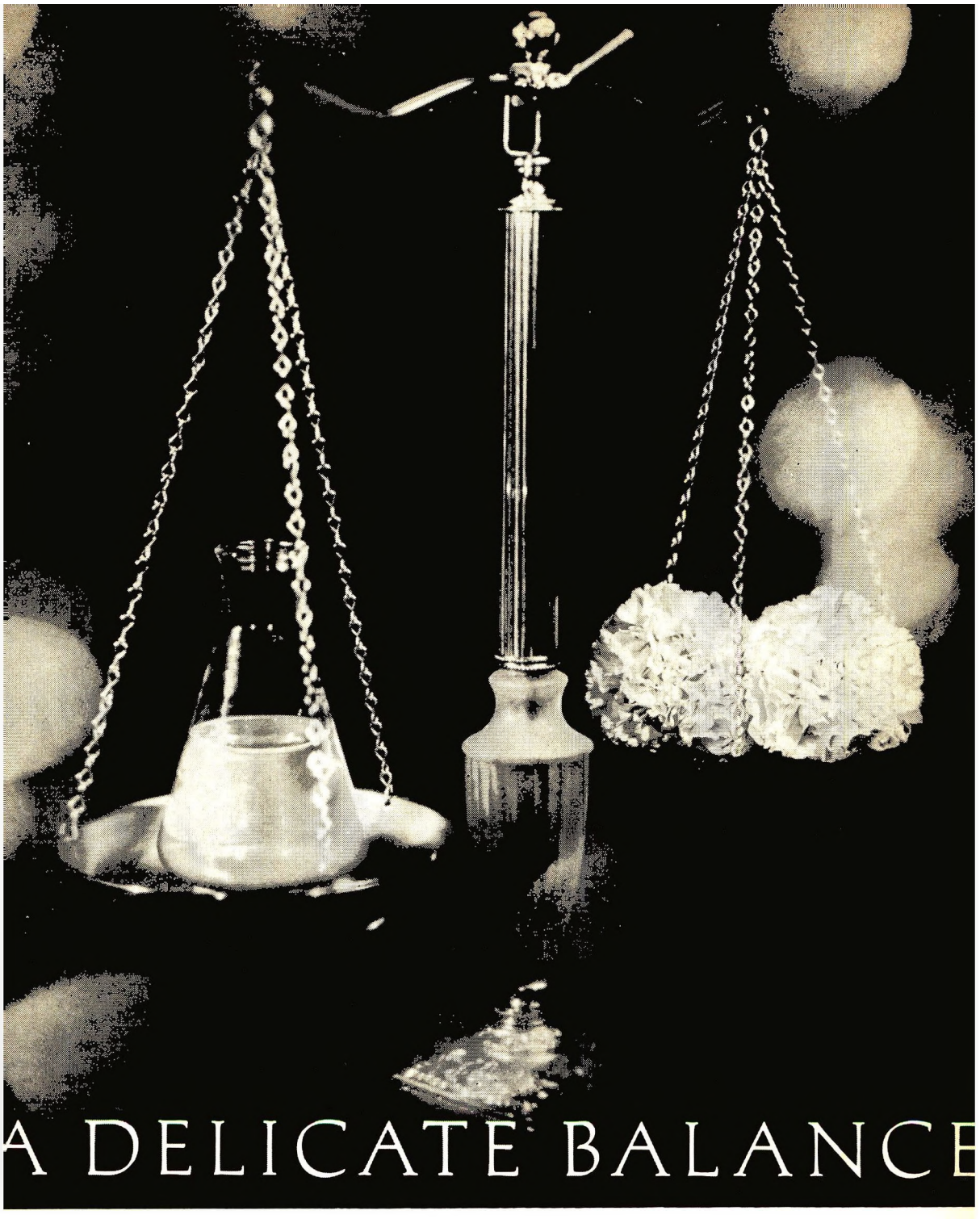

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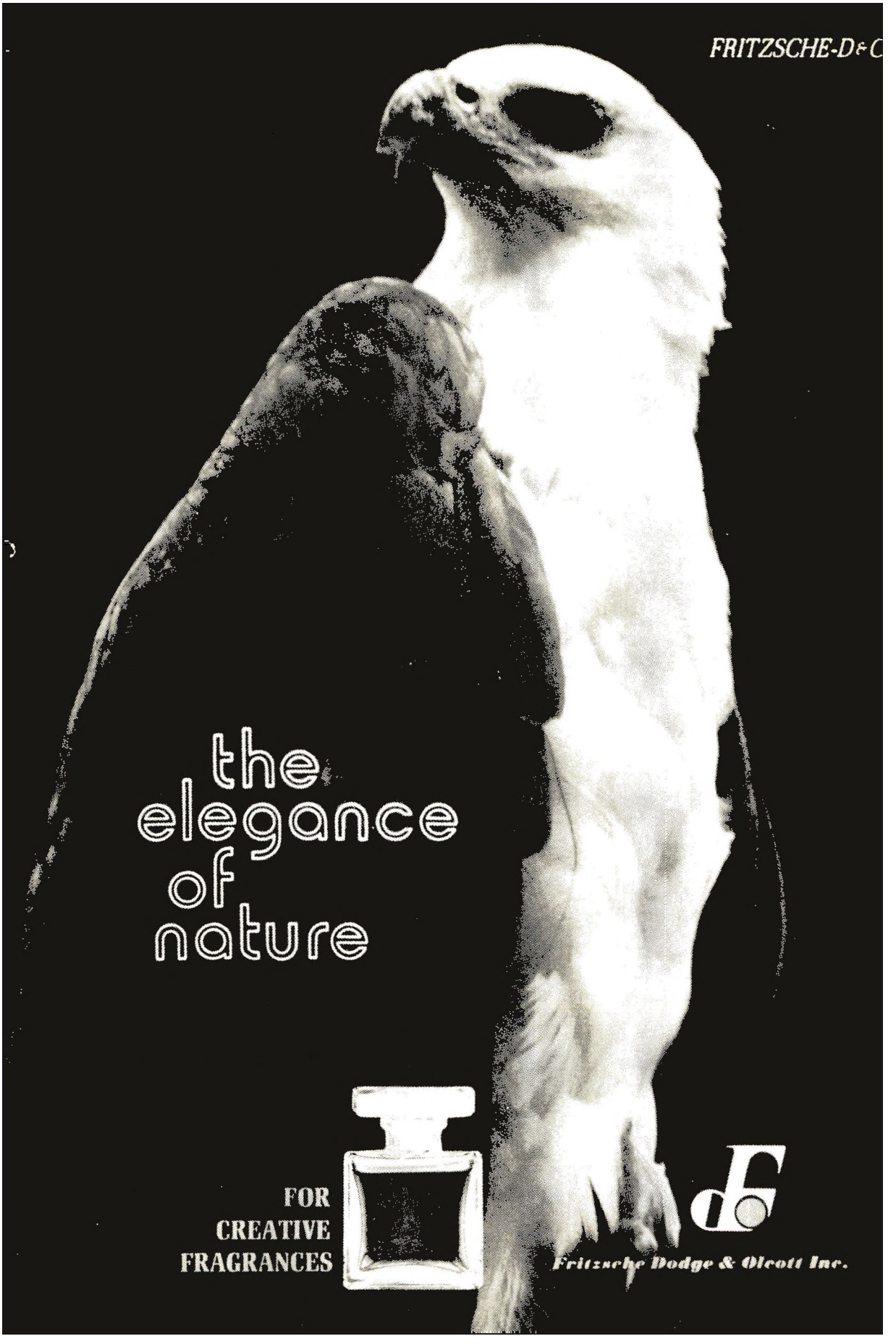
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