

## STUDIES OF SKIN REACTIONS TO PROPYLENE GLYCOL.\*

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The present report deals with our observations of reactions of the human skin to externally applied propylene glycol.

We believe that our topic is of practical importance, since propylene glycol has found steadily increasing usage as a constituent of the bases of many different pharmaceutical preparations and cosmetic articles. During the last decade, it has found employment also as a "simple effective aerosol for the sterilization of air", largely as a result of the studies by Robertson et al. (1).

Propylene glycol, first described by Wurtz in 1859, (2), is a dihydric alcohol which has 2 isomers, the more common represented by the formula:  $\text{CH}_3\text{-CHOH-CH}_2\text{OH}$ . It is a colorless, odorless liquid, readily miscible with water, and more viscous than water (viscosity of propylene glycol about 2.18 centipoises; that of water 1.79 centipoises at 0°C).

Numerous toxicologic studies carried out by different investigators during the last 20 years (3, 4, 5, 6, 7, 8, 9, 10, 11, 12) have revealed a low toxicity of propylene glycol. Several of the investigators (3) (4) (12), however, observed considerable, though transitory, inflammatory reaction of the tissues at the site of subcutaneous or intramuscular injection. Upon external application of undiluted propylene glycol to certain mucous membranes, namely of the human tongue, and of the rabbit's eye (conjunctiva), Seidenfeld and Hanzlik (3) noted a fleeting local irritation. The authors explained this response on the basis of "hypertonicity" of the undiluted glycol. "Isotonic" solutions of propylene glycol (2.5% in water) failed to produce any inflammatory reaction of the rabbit's conjunctiva.

Our present study was prompted by a chance observation of positive skin reactions to propylene glycol in a series of patients in which the agent was employed as a solvent for potentially allergenic materials.

### METHOD

From April 1951 to April 1952, propylene glycol was applied in "orthodox" ("closed" or "covered") patch tests to grossly normal skin of 866 patients. This group comprised subjects who attended the Section of Allergy at the New York Skin and Cancer Unit because of various dermatologic conditions. The test sites were examined 48 hours after application of the patches.

In the early phase of the study, additional tests were performed in which the propylene glycol patch was covered by layers of gauze over the cellophane, rather than by the ordinary Elastoplast bandage. This was done to eliminate the possi-

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bility of a positive skin reaction produced by materials extracted from the adhesive.

In order to recognize positive skin reactions which might be caused by accidental contamination of a given sample, simultaneous tests were carried out in 84 of the subjects with two or more samples of "purest grade" propylene glycol, supplied by different manufacturers.

A group of the patients was tested also with 50%, 10%, and 2.5% dilutions of propylene glycol in water. In addition patch tests were performed with chemically related compounds: glycerine, and carbowax 1500, a polymer of polyethylene glycol.

Propylene glycol was also applied in some of the individuals by simple inunction, in order to compare the response of uncovered skin with the result of the patch test. The inunction was carried out for 20 seconds by means of the rounded end of a glass rod.

In many of the patients the patch tests were applied repeatedly, but in different areas, and when possible, the individuals were re-tested after a lapse of several months.

Patch tests with propylene glycol were performed in several of the reactors following a standardized method of exposure to dry heat (reflector-type sweat box (13) (14)), and the results were compared with those obtained prior to heating.

A number of female reactors received lipsticks containing propylene glycol for trial usage.

#### RESULTS

Positive skin reactions to patch tests with propylene glycol were observed in 138 (15.7%) of the 866 subjects tested during the past year. These reactions ranged from simple erythema (+) to erythema with induration and vesiculation (+++). Eighty-nine of the 138 patients with a positive reaction attended the clinic because of dermatitis venenata.

Of the 84 individuals who were subjected to simultaneous testing with several samples of propylene glycol from different sources, 15 showed a positive reaction. In none of these was there any difference whatsoever in the response to the different brands of propylene glycol.

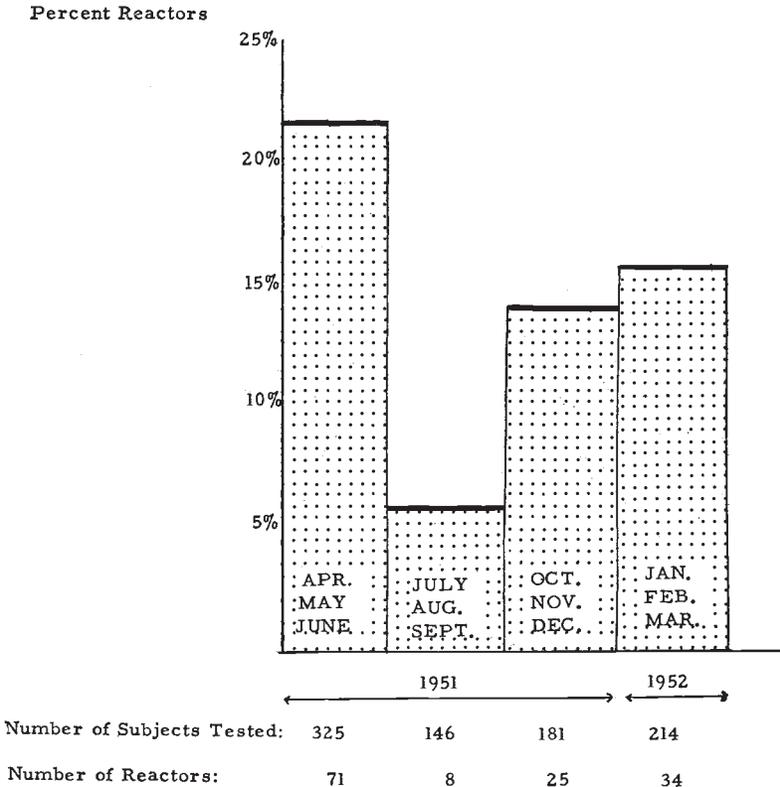
Twenty-three persons with positive reactions to pure propylene glycol were tested also with 50% and 10% dilutions in water. In general, the intensity of the positive reactions decreased as the concentration of the agent was decreased. In only five instances was a positive response (erythema, "+") elicited by the mixture containing 10% propylene glycol. A 2.5% dilution was applied in only three of the subjects, and produced a positive result in one instance.

In 16 subjects who showed a positive reaction to propylene glycol, patch tests were applied likewise with glycerine and with carbowax 1500. In one of these subjects a positive reaction was obtained with carbowax 1500, and in a second subject a doubtful reaction with the glycerine.

Sixteen of the patients exhibiting a positive response to propylene glycol with

the closed patch test were tested also by simple inunction of the agent. In no instance was there any evidence of an inflammatory response to the inunction either shortly after the application, or 48 hours later.

The incidence of positive reactions to propylene glycol appeared to show a seasonal fluctuation, inasmuch as the incidence was at its minimum during a period of hot and humid climate (New York City: July, August, September 1951), and significantly higher during the cooler and less humid seasons.



GRAPH I. Incidence of positive patch test-reactions to propylene glycol

The fluctuation is demonstrated by our graph (I) which shows a significant drop in the number of positive reactions during the three above mentioned summer months.

In 23 of the reactors, the patch tests with propylene glycol were repeated after a lapse of from 2 to 12 months after the first testing. Seventeen of these subjects again showed a positive response, whereas the remaining six did not. In three of these six individuals, the reaction was negative on re-testing at higher environmental temperature and relative humidity. The remaining three subjects, however, showed a change of the response to negative despite a change of the atmospheric conditions toward lower temperature and humidity.

Following our heating experiment, two of three reactors subjected to the procedure showed a distinct reduction in the intensity of the reactions to propylene glycol, as compared with the patch test results observed prior to the stimulation sweating. The actual findings obtained in these experiments are listed in the table below:

TABLE I  
*Patch test response to propylene glycol after thermal sweating*

SUBJECT	MATERIAL TESTED	NUMBER OF WEEKS PRIOR TO EXPOSURE TO HEAT:				REACTION "IMMEDIATELY" PRIOR TO EXPOSURE TO HEAT	REACTION FOLLOWING EXPOSURE TO HEAT
		13	7	4	2		
J. B.	<i>Propylene Glycol: undiluted</i>						
	Brand A*			+++	++	++	+(+)
	Brand B†				++	++	+(+)
	Brand C‡						+(+)
	<i>Propylene Glycol: (Brand A) diluted with water</i>						
	50%				++	++	-
10%					(+)	-	
2.5%					+	-	
M. A.	<i>Propylene Glycol: undiluted</i>						
	Brand A				++	+(+)	+
	Brand B						+(+)
	Brand C						+
	<i>Propylene Glycol: (Brand A) diluted with water</i>						
	50%						-
10%						-	
2.5%						-	
E. W.	<i>Propylene Glycol: undiluted</i>						
	Brand A	+(+)	+(+)			+(+)	(+)
	Brand B					+	(+)
	Brand C					+	(+)
	<i>Propylene Glycol: (Brand A) diluted with water</i>						
	50%					+	(+)
10%					(+)	-	
2.5%					-	-	

\* Brand A, obtained from Magnus, Mabee and Reynard, Inc., New York, N. Y.

† Brand B, obtained from Carbide and Carbon Chemical Corp., New York, N. Y.

‡ Brand C, obtained from Fisher Scientific Corp., New York, N. Y.

Fifteen female subjects who had shown a positive skin-reaction to propylene glycol patch tests were observed while using lipsticks containing propylene glycol. No abnormal response was observed in 14 of these subjects, whereas one developed a distinct, exfoliating cheilitis within three days of usage of the lipstick. Her skin reaction, however, was negative when the material of the lipstick was applied by patch test.

The fact that nearly 65% of the total number of reactors suffered from "dermatitis venenata" of one origin or another—at least during the beginning phase of their clinical attendance, cannot be ignored. Concomitant but subclinical changes of the entire skin might essentially contribute to the inflammatory patch test response to propylene glycol.

In view of the fact that propylene glycol strongly tends to attract water and to cause dehydration, it would appear possible that the inflammatory test reactions are the result of excessive attraction of water from the skin by the agent on its surface. This hypothesis is supported by our observations suggesting a greater tendency to positive reactions during periods of low environmental temperature, and of low relative humidity (fall of dew point), i.e. at times when there is an increased tendency to desiccation of the skin surface by environmental factors. Evidently, the climatic factors during these periods are precisely the same which are responsible for the development and/or recurrence of "chapping" and related lesions of the skin, such as "winter itch", nummular eczema, etc. Only recently Gaul and Underwood (15) have demonstrated that the skin changes of this category tend to develop below certain "critical" levels of the dew point and dry bulb temperature.

The distinct decrease of the skin's reactivity to patch tests with propylene glycol, observed by us after exposure to dry heat in two of three reactors we have studied in this regard, lends further support to the assumption that hydration of the skin surface diminishes this form of hypersensitivity. The experimentally stimulated outpouring of sweat apparently results in a "protective" imbibition of the surface layers of the skin, similar to that produced by a warm and humid atmosphere. Recent investigations by our group suggest that, in addition, augmented sweat delivery physiologically leads to an increase in the amount of ether-soluble material (chiefly sebum) on the skin surface. Obviously this effect also may well contribute to the increased tolerance of the skin for the tests with propylene glycol.

It seems interesting and important for practical reasons that we did not observe any irritation from the "open" testing, i.e. the inunction of propylene glycol on the skin of subjects who showed a positive reaction to the covered patch test. Fortunately, externally applied products containing propylene glycol are usually applied without any form of occlusive dressing. It is for this reason that the skin's tolerance for such products was generally tested in the manner of "intended usage", by simple inunction. The occurrence of skin-hypersensitivity to propylene glycol has not come to light heretofore possibly for the same reason. In extensive earlier investigations, for instance, carried out in this Department (16) (17) with liquid preparations containing propylene glycol, as well as with propylene glycol alone, the method of testing was essentially confined to "open" inunctions. The absence of inflammatory reactions was interpreted as evidence that propylene glycol was innocuous.

The possible significance of the observation that one of our 15 female subjects with positive patch tests to propylene glycol also suffered a cheilitis from a propylene glycol containing lipstick, while the other patch test positive subjects had no cheilitis from such lipsticks, will be studied further.

## DISCUSSION

The fact that positive reactions were obtained with patch tests with propylene glycol and that the incidence of these reactions was high, appears noteworthy and of possible practical significance.

We have been unable to decide whether the reactions were allergic in nature or due to primary irritation. The assumption of a primary irritation seems to find support in our observation that only 5(21%) of the 23 subjects with a positive response to the undiluted material exhibited a reaction to the 10% dilution.

Moreover, the great fluctuations in the incidence of positive reactions in general, as well as the relatively considerable proportion of subjects in whom positive and negative reactions were obtained at different times can hardly be explained on the basis of a specific allergic contact-type hypersensitivity.

## SUMMARY

1. Undiluted propylene glycol produced positive patch test reactions in 138 (nearly 16%) of 866 subjects, who attended the clinic because of various allergic, or possibly allergic dermatoses.

2. Although it was impossible to decide whether or not the positive reactions to propylene glycol were due to specific sensitization, it appears more likely that they were caused by "primary irritation".

3. It is suggested that excessive dehydration of the skin may be an important factor predisposing to the reactions.

4. In conformity with this assumption, the incidence of inflammatory responses was at its minimum during the hot and humid season, and high during periods of low environmental temperature and humidity, when there is normally a greater tendency to dehydration of the skin's surface tissues.

Similarly, a distinct reduction in the intensity of the patch test response was observed in two of three subjects tested after stimulation of sweating by exposure to heat.

5. In one of the patients who reacted to patch tests with propylene glycol, a cheilitis developed upon use of a lipstick containing propylene glycol. The significance of this observation remains to be elucidated.

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## DISCUSSION

DR. SAMUEL M. PECK, *New York, N.Y.*: Dr. Warshaw presented us with a beautiful example of how to use judgment in doing a patch test. Here she was dealing with a primary irritation and that is why she got the difference between the actual use of the substance and the patch test.

DR. ADOLPH ROSTENBERG, JR., *Chicago, Ill.*: I would like to commend Dr. Warshaw and make one suggestion. Dilute this substance with glycerine. If then the same number of reactions occur, it would be a stronger argument that they are on a primary irritant basis. I would recommend that all of you read the fine article from the Army Industrial Hygiene Laboratory on the study of the influence of environmental factors on patch test reactions.

DR. LEO ORRIS, *New York, N. Y.*: In the May 1, 1952 issue of the *Journal of Experimental Medicine*, there is a paper by Dr. Eisen, Belman and myself on the "Elicitation of Delayed Allergic Skin Reactions with Haptens." In this work, we have demonstrated that those compounds which elicit a reaction in an animal or human sensitized to that or a structurally related compound, combine *in vitro* with skin protein through the formation of bonds of the co-valent type. The homologues of these compounds which are unable to elicit a reaction, do not combine with protein. It is this factor, therefore—skin protein combination—which apparently is a primary prerequisite for eliciting a reaction in a sensitized individual. This explains why compounds structurally similar do not react *in vivo*.

DR. MARION B. SULZBERGER, *New York, N. Y.*: In reference to Dr. Orris' remarks and work, may I call his attention to the investigations of Landsteiner and collaborators (*J. Exper. Med.*, **61**: 643-656, May 1935) and particularly of Rostenberg and Kanof (*J. Invest. Dermat.* **4**: 505, Dec. 1941) and of Baer and myself (*J. Invest. Dermat.* **1**: 45, Feb. 1938) demonstrating that the capacity of these different compounds to conjugate with bases (their alkali-lability) ran parallel to their allergenic capacity for the skin; including eczematous contact-type sensitivity. We had shown some time ago on human volunteers that in the particular group of compounds which Orris and Eisen have now again employed, those members which would be most readily capable of conjugating with the proteins were precisely those most capable of eliciting contact-type eczematous sensitivity when applied to the human skin.

DR. THELMA WARSHAW, *New York, N. Y.*: I wish to thank the discussors. In answer to Dr. Rostenberg's suggestion, I should like to point out that propylene glycol is more hygroscopic than glycerine. Under standardized conditions, water attraction causes a weight increase of propylene glycol up to about 35%; of glycerine, up to about 28%. We think this difference in affinity for water may account for the observed difference in the reactions.

Since the degree of water attraction by mixtures of glycerine and propylene glycol is presumably intermediate between the attraction by each of these liquids alone, interpolated degrees of the skin reactions might be expected from test applications of the mixtures.