CONTACT DERMATITIS FROM RUBBER CAUSED BY ALLERGIC SENSITIVITY TO THIO-BETA-NAPHTHOL*

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Although numerous reports on allergic epidermal sensitivity to rubber have appeared in the literature (1–26), in only relatively few cases has the sensitizing agent been identified (Table I). The task is difficult because of the wide variety of different rubber products and the numerous compounds introduced in the manufacturing process. Antioxidants, accelerators, peptizers, vulcanizers, fillers, extenders, softeners, preservatives, tackifiers, plasticizers, and stabilizers, many of them allergenic chemicals, are added to improve the quality and durability of the rubber.

The present report deals with a case of epidermal allergic hypersensitivity to rubber which was traced to thio-beta naphthol (2-naphthalenethiol 2-sulfhydryl naphthalene, beta naphthylmercaptan). To the best of our knowledge, this chemical has not been reported previously as a sensitizer in rubber. In an attempt to identify the reactive groupings which were responsible for the epidermal hypersensitivity, we tested numerous other compounds related to thio-beta naphthol for their allergenic properties. We also studied the effect of cortisone on the epidermal sensitivity.

CASE REPORT

H. H., 51 year old white male baker, when first seen in the Dermatology Clinic of the Philadelphia Veterans Administration Regional Office in May, 1950, had had severe asthma for the previous six years. Skin tests had indicated a sensitivity to dust, duck feathers and timothy; and intracutaneous desensitization to dust and timothy grass had been carried out in the Allergy Clinic for the previous six months. Inasmuch as the patient developed untoward side effects from epinephrine and ephedrine, his main reliance for symptomatic relief from asthma were injections of aminophylline. He estimated that he had received approximately 150 such injections in the preceding six years. During the past year, on about six occasions he had noted a mildly pruritic skin reaction at the site of application of the tourniquet following intravenous injections of aminophyllin in both the Veterans Administration Allergy Clinic and in his local hospital. He believed that this reaction occurred only when an orange tourniquet was used, but not following the application of a black tourniquet. There was no history of previous cutaneous reaction to other rubber articles, such as adhesive plaster, condoms, garters, or to shoes. A black rubber tourniquet was applied for 15 seconds to one arm; and to the other arm, the orange rubber tourniquet which had been used for the injections at the Veterans Administration Clinic was applied for 15 seconds. Eleven hours after the application, the patient noticed a reaction only at the site of the orange tourniquet. When seen twenty four hours later, a sharply outlined band of erythema with tiny vesicles was visible at this site (Fig. 1.).

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TABLE I

Substances in rubber causing allergic epidermal sensitivity

Accelerators

1. Mercaptothiazole type

2-mercaptobenzothiazole (20, 22, 24, 26)
2,2 benzothiazyl disulfide (26)
Zinc benzothiazyl sulfide (26)
2-Benzothiazole sulfenamide (26)
3-(2-Methylphenyl)-benzothiazolydene-2-thione (26)

2. Dithiocarbamyl type

Tetramethylthiuram monosulfide (24, 26)
Tetramethylthiuram disulfide (19, 22, 24, 26)
Selenium dimethyl dithiocarbamate (26)
N-pentamethyleneammonium pentamethylenedithiocarbamate (26)

3. Miscellaneous

Hexamethylenetetramine (18, 22, 24)
Guanidine (24)
o- and p-Toluidine (24)
Triethyltrimethylenetriamine (18, 24)
2,4-Diaminotoluene (22)
Hexadinitrophenylamine (22)
Diphenylguanidine (20)
Methylene aniline (18)
p-Nitroso-N-dimethylaniline (18)
p-Phenylenediamine (18)
Butyraldehyde-aniline condensation product (26)
Safex (18)
B.B. accelerator (18)

Antioxidants

N-Phenyl-beta-naphthylamine (18, 22, 23, 24)
N-Phenyl-alpha-naphthylamine (22, 26)
p-Benzyloxyphenol (24, 26)
Polymerized trimethyldihydroquinoline (26)
Reaction product of diphenylamine and acetone (26)
p-Nitrosoaniline (22)

Peptizing agent (also antioxidant)

2-Naphthalenethiol (Thio-beta-naphthol) (present study)

Finished rubber products

Neoprene (21)
Thioprene (25)

This patient has been under close observation by one of us (I. L. S.) for two and a half years. On one occasion he experienced dermatitis on the wrist following the wearing of a heavy rubber glove. Except for miliaria, due to excessive sweating from working as a baker in a hot environment, he has presented no other cutaneous disease. By requesting application of the black tourniquet for his intravenous injections, he has avoided further cutaneous manifestations such as brought him to our clinic. His asthma has continued unabated.

EXPERIMENTAL STUDIES

The orange tourniquet was extracted with acetone, and the allergenic factor was present in the extract and not in the residue. He was then tested with a variety of other rubber articles, (erasers, stoppers, gloves, rubber bands and

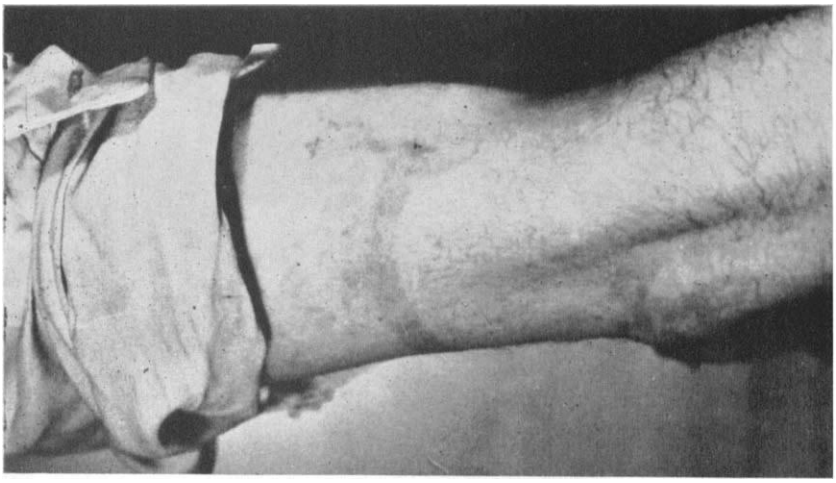

FIG. 1. Band of erythema with vesicles 24 hours after application of rubber tourniquet for 15 seconds.

various kinds of tubing), but reacted only to two samples of blood count pipette tubing.

The source of the orange rubber tourniquet could not be discovered. However, with the assistance of Dr. Louis Tuft, Consultant in Allergy, Philadelphia Veterans Administration Regional Office, another piece of rubber tubing, similar in appearance to the original one was obtained from the Veterans Administration Supply Depot, and the patient also reacted positively to this sample. This tubing was the product of the Davol Rubber Company, Providence, Rhode Island. The manufacturers were most cooperative in helping to trace the allergenic agent. The tubing was made of natural rubber and contained rubber clay, whiting, zinc oxide, iron oxide, sulfur, N-cyclohexyl-2-benzothiazole as an accelerator, a diphenylamine compound as an antioxidant, and "RPA2" (thio-beta-naphthol) as a peptizing agent. The peptizing agent was suspected as the allergen by the manufacturers, who stated that it was not used in rubber articles which came in contact with the skin. This agent, thio-beta-naphthol, was found to cause an erythematous reaction when 0.025 cc. of a 1:1000 concentration (25 micrograms)

in xylene, acetone or ethyl alcohol was applied to the skin. In the course of repeated testing over a period of two years, reaction to rubber appeared 8 to 24 hours after application, whereas reaction to solutions of thio-beta-naphthol appeared in 1 to 7 hours. Thio-beta-naphthol in xylol, allowed to stand tightly stoppered for 14 days, caused no reaction, apparently because of rapid oxidation of the allergenic agent in solution. Such oxidation is prevented for long periods of time in the rubber tubing itself by the antioxidant present. However, 21 months after we first observed this patient, the original tourniquet (age unknown) no longer provoked a reaction, although the reaction to thio-beta-naphthol in

TABLE II

Negative cutaneous reactions to "drop" and patch tests

1. Residuum following acetone extraction of offending tourniquet
2. Neoprene (2-chloro butadiene)
3. Butadiene acrylo-nitrile co-polymer (Hycar OR 15) (synthetic rubber)
4. Polystyrene latex (synthetic rubber)
5. Natural rubber dust (from reclaimed rubber)
6. Natural rubber, smoked sheets, steam distilled
7. Zinc butyl xanthate
8. n-Butyl amine
9. Triethyl trimethylene triamine
10. P-tertiary butyl catechol
11. Tetramethylthiuram disulfide
12. Tetramethylthiuram monosulfide
13. 2-Mercaptobenzothiazole
14. Phenyl beta-naphthylamine
15. Thiophenol
16. Thio-alpha-naphthol
17. Benzyl mercaptan
18. Cetyl mercaptan
19. Dodecyl mercaptan
20. Thiosorbitol
21. Beta naphthol
22. Lead salt of thio beta naphthol
23. Copper salt of thio beta naphthol

solution was still positive, indicating oxidation of the thio-beta-naphthol in the rubber tubing over a period of years. The manufacturers advised us that thio-beta-naphthol is present in the finished rubber tubing in a concentration of 0.1875% or less and is used to facilitate smooth extrusion of the tubing.

Through the cooperation of E. I. duPont de Nemours and Co., manufacturers of the peptizing agent, closely related thio compounds were made available for testing*. No reaction could be elicited from any of these compounds when they were tested in a 1:50 concentration. The lead and copper salts of thio-beta-naphthol, prepared by the method of Billeter (27) and Schertel (28) when applied

* The authors are greatly indebted to Dr. Madison Hunt, Jackson Laboratory, E. I. duPont de Nemours and Co., for his cooperation in providing us with samples of rubber ingredients.

as patch tests for 48 hours, elicited no reaction. All solutions were made up in 95% ethyl alcohol immediately before testing. Except for the two salts referred to above, all tests were carried out by dropping approximately 0.025 cc. of the solution on the skin or by applying it to a small area with a cotton tipped applicator. No covering was applied. Table II lists the chemicals to which the patient failed to react on cutaneous testing.

Intracutaneous injection of 0.2 ml. of 1:100 cysteine and of 1:100 glutathione did not inhibit the reaction to thio-beta-naphthol applied on the injected sites 5 minutes later.

Cortisone was administered orally in doses of 50 milligrams every six hours for three days. Table III demonstrates the results of skin testing with various dilutions of thio-beta-naphthol 48 hours after the start of cortisone. Tests were read after 24 hours and revealed a moderate diminution in reactivity.

TABLE III

Effect of cortisone on epidermal allergic reactivity to thio-beta-naphthol

DILUTION OF THIO-BETA-NAPHTHOL IN ALCOHOL	BEFORE CORTISONE	AFTER CORTISONE (50 MG. EVERY 6 HRS. FOR 72 HRS.). TESTED AT 48, READ AT 72 HRS.
1:50	+	+
1:75	+	+
1:100	+	−
1:200	+	−
1:400	−	−
1:1600	−	−

DISCUSSION

This case presents an example of the highest degree of specificity to an allergenic agent. Any alteration in the configuration of the thio-beta-naphthol molecule abolished the allergenic properties of the compound. Both the naphthol and the sulfhydryl parts were essential to produce the reaction. Since the free sulfhydryl group is the most reactive part of the molecule, it is probable that the allergen combined with the epidermal proteins by means of this group. Alteration of the sulfhydryl group by salt formation (copper or lead salts) or by shifting this group to a less accessible position (thio-alpha-naphthol) resulted in the disappearance of the allergenic properties (Fig. 2).

It was thought that thio-beta-naphthol acted by displacing the naturally occurring sulfhydryl amino acid, cysteine. However, intracutaneous injection of an excess of cysteine did not prevent the development of the reaction to thio-beta-naphthol. This test must be considered as crude and negative results cannot be interpreted as an indication that thio-beta-naphthol does not displace cysteine when it combines with the epidermal proteins. We are only allowed to conclude that under the experimental conditions used, cysteine did not prevent the epidermal allergic reaction.

The finding that cortisone decreases the epidermal sensitivity to high dilutions of the allergen is in agreement with observations made by previous authors (29).

It has been stated recently that "between 1000 and 1500 different chemical entities go into the production of finished rubber. Moreover, there are many variations of rubber and the end product of rubber manufacture seems to result in substances that are different from any of the component parts" (17). While we do not underestimate the difficulty involved in identifying the sensitizer in a rubber product, success may often be attained. In a recent study Blank and Miller tracked down the offending allergens in 17 of 24 patients with dermatitis of the feet caused by sensitization to rubber adhesives in shoes (26). Many manufacturers are helpful and cooperative in supplying competent investigators with information concerning the compounds used in their products and with samples for patch testing. In addition, there have been enough common sensitizers described (Table I), to warrant trials with at least these well-known offenders. To gain further information concerning the nature of epidermal hypersensitivity and to determine whether or not sensitivity patterns can be correlated with

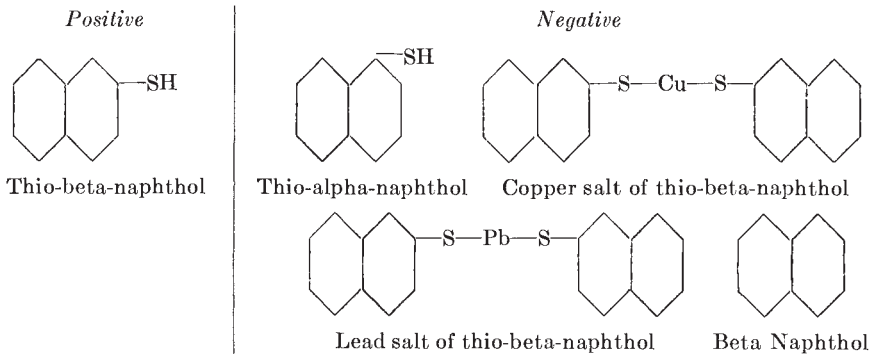

FIG. 2. Epidermal reaction to thio-beta-naphthol and related compounds

chemical structure, it is essential to detect the allergen so that the reactivity of the epidermis to chemically related compounds may be studied.

SUMMARY

1. A case of contact dermatitis from natural rubber is described. The patient reacted with erythema and vesicle formation to the application of a rubber tourniquet for as little as 15 seconds.

2. The allergenic factor was identified as the peptizing agent thio-beta-naphthol. The patient responded with an erythematous reaction to the application of as little as 25 micrograms of the pure chemical.

3. Several dozen other related compounds were tested with negative results. Some of these were thiol compounds; others were derivatives of alpha and beta-naphthol. A high degree of specificity to the allergenic agent was demonstrated.

4. Hypotheses concerning the mechanism of the reaction are presented.

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DISCUSSION

DR. SAMUEL M. PECK, New York, N. Y.: Dr. Schamberg emphasizes several points which we have noted in our experiments (Cross-Sensitivity as a Factor in Chronic Recurrent Dermatoses, Comp. Med. Dec. 1949, Vol. 2, No. 4 and N. Y. St. Jour. Med. Vol. 50, No. 22, Nov. 15, 1950). The cross-relationship must be based on the strength of the individual compounds as antigens for allergic phenomena. A greater readiness to cross reaction with more distantly related compounds will be produced primarily by the stronger allergens.

DR. ADOLPH ROSTENBERG, JR., Chicago, Ill.: I think we have heard three interesting papers in the general field of hypersensitivity. All papers concerned themselves with one aspect of the important problem of sensitivity and that is specificity. There is another important aspect I want to touch on—the genetic makeup of the individual. Why do some people have sensitivity and why is this directed toward certain chemical substances? Why, for instance, did Dr. Schamberg's patient become sensitive to thio-beta-naphthol when others who had equal opportunity to encounter this substance did not become sensitized? We cannot answer that question but it is well to remember that, in addition to the compound, the individual plays an equally important role.

I would like to give one word of warning. Dr. Schamberg reported on one case. It is hazardous to talk about specificity on the basis of one individual because one will find in a group of individuals sensitive to a given allergen that there is considerable variation in that group.

The work reported today again confirms that in order to elicit sensitivity the compound has to combine with tissue proteins.

I would disagree with Dr. Peck concerning the difference between nucleus and side-chain reactions. If the compound unites by means of a side-chain, then there will be cross-reactions with other compounds which form unions of a similar chemical nature. In sensitizations to the dinitrohalobenzenes there are reactions between all the halogens because the halogen merely acts as a tool by which the compound can unite.

DR. RUDOLF L. BAER, New York, N. Y.: In connection with Dr. Schamberg's paper, I would like to point out that there is one thiocompound which has a very high sensitizing capacity after topical application, namely BAL (Dithiopropanol). Some years ago Drs. Sulzberger and Kanof and I showed that about 19 per cent of those exposed to topical application of 5% BAL ointment on normal skin and 66% of those exposed on burned skin develop an allergic sensitization to this compound.

One of the most interesting features of Dr. Schamberg's paper was that the skin response came on very early i.e. within a few hours. In our publication (J. Clinical Investig. **25:** 488, 1946) we pointed out that the allergic sensitization to BAL seemed to be intermediate between the urticarial and the eczematous type.

It may be worth mentioning here that in many cases of sensitization to rubber

gloves, the dermatitis is due to chemicals which contain an amino group in the para position on the benzene ring and which thus produce a wide spectrum of cross sensitizations. We had observed this clinically, but detailed studies on this subject have been done by Sidi.

Dr. Schamberg should be commended for having carried out an attempt to study the cross sensitizations in his patient. I believe that future progress in the field of allergic eczematous contact-type sensitivity will be made to a large extent through such studies. If we wish to practice preventive medicine we should try to instruct our patients in regard to those compounds which might cause difficulties because of their immuno-chemical relationship to a compound to which the patient is known to be allergic. However, I agree with Dr. Rostenberg's remarks (in his discussion of the paper by Warshaw & Herrmann) that the sensitivity spectrum of one individual might be entirely different from that of the next subject, even though they have become sensitized to the same substance. We found this to be true when we patch tested a large series of patients who had allergic sensitizations to compounds which have an amino group in the para position on the benzene ring, with an extensive series of chemically related compounds.

Dr. Stephen Rothman, Chicago, Ill.: How can it be explained that the rubber containing 0.1 % of the offending material caused violent reactions whereas in the quantitative patch test the threshold concentration (obviously causing just perceptible reaction) was 1:200 or 0.5 %? Were normal persons patch-tested and how many?

Dr. Peter Flesch, Philadelphia (inclosing): Dr. Rostenberg's objection that we have tested only one individual is valid. However, we must begin somewhere and our approach would seem to be more fruitful than the continued barren clinical descriptive papers. There is no doubt that more cases have to be studied before we can reach definite conclusions.

In answer to Dr. Rothman, we have patch-tested normal people and they did not react. The objection that a thiol group on an aromatic nucleus is different from an alkyl-bound —SH group, is valid. As for the concentration of the substance, the patient reacted at times to a 1:1000 concentration which compares favorably with the concentration reported to occur in the rubber.