METHYLOCTYLBENZENESULPHONATE: A NEW INDUSTRIAL SENSITIZING AGENT

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Occasional outbreaks of dermatitis caused by allergic reactions to chemicals occur in industry (Squire, Cruickshank, and Topley, 1950). For example, the sensitizing properties of the explosive "tetryl" are now well recognized, while on a smaller scale the manufacture of pyrethrum powder gives rise to a large proportion of sensitization rashes among exposed workers (Martin and Hester, 1941). Schwartz, Tulipan, and Peck (1947) provide a long list of substances with sensitizing properties. This paper describes an outbreak of skin disease which was found to be due to a chemical sensitizing agent not previously recognized.

Early in 1951 a new process was begun for the preparation of a highly charged compound, methyltriethylammoniumoctylbenzenesulphonate, for incorporation in an antistatic lubricant. This material was produced originally in a pilot plant and it happened that several chemical engineers exposed to it developed acute transient skin rashes and swelling of the eyelids and lachrymation. The final material is produced in five stages, and the workers concerned held the opinion that the skin troubles were due to some agent in stage 4 of the process.

In stage 4 the following reaction is carried out :

This reaction is carried out in the presence of carbon tetrachloride and is aided by heat. The crude ester so formed is a dark brown, tarry liquid which is subsequently washed by a counter-current

of water in a wash column. The crude material is very acid and so is liable to cause primary irritation or burns.

Of the other chemicals concerned in this process, octylbenzene is a relatively inert material, carbon tetrachloride is a skin irritant with well known toxic properties, while methylchlorosulphonate is a highly reactive material extremely irritating to the skin. The vapour of this substance causes acute lachrymation and congestion of the nasal mucosa.

However, as the symptoms of the workers and the history of the outbreak were strongly suggestive that the trouble was due, not to primary skin irritation, but to the development of hypersensitivity, investigations were made to determine whether any of the substances involved were sensitizing agents.

Clinical Findings

In all 10 persons had been engaged at one time or another upon the process and all of these had suffered from skin rashes of varying severity. Usually in association with the rash the workers complained of "pricking" of the eyes, swelling of the lids, and lachrymation. Occasionally these symptoms occurred without any accompanying skin trouble. The dermatitis was usually vesicular but sometimes only erythematous. It was associated with intense irritation and local swelling of the subcutaneous tissue. The workers involved stated that the rashes usually followed skin contamination with the crude ester but not infrequently no such incident could be recalled. The majority of rashes occurred for the first time between the second and third month of duty, but in one instance started after five weeks.

The case histories of three workers are described below ; these illustrate the principal clinical features.

Case Reports

Case 1 (E.O.).—This chemical engineer started work on this process in May, 1951. In July, he spilled a solution of the ester upon his arm. He washed at once but during the next 24 hours he developed an irritating vesicular rash on the contaminated area, and the eyelids became swollen. The dermatitis healed in a fortnight. Following this incident his job was changed owing to reorganization in the department, and he no longer came into close contact with any of the materials.

In August, 1951, the patient was on holiday when he suffered from an outbreak of the rash on the area originally affected and he also developed eye symptoms similar to those previously experienced. He then realized that he had put on the shirt which had previously been contaminated with the ester. This shirt had been laundered but had not been worn since the original episode.

Case 2 (L.O.).—This patient first worked on the process in August, 1951. After five weeks he developed an eczematous rash on both forearms ; he had never at any time to his knowledge spilled any of the materials upon the skin. Not until July, 1952, did he experience any eye symptoms, but at this time the eyelids became swollen with lachrymation. He has remained on the process and has had no serious outbreak of skin trouble since his first attack. He states that he gets an occasional erythema of the arms in the evening but this is gone by the next morning. He is also under the impression that his skin has become much drier since working on this job.

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Case 3 (J.W.T.).—This worker started work on this process in July, 1952, and had no trouble in the ensuing seven weeks. In August, however, he spilled some of the crude ester upon the arms. He did not attach much importance to this, but during the next 24 hours a severe dermatitis occurred on both the forearms (Fig. 1).

FIG. 1.—Vesicular rash on forearm caused by contact with methyloctylbenzenesulphate.

This was vesicular and was associated with gross oedema and erythema of the whole of the forearm. The arms were extremely itchy and in the course of the following 24 hours the eyelids swelled and the eyes became irritable. The swelling was so great as to obscure his vision completely. The dermatitis remained in an active condition for some four days, and in addition to the sites originally affected, patches of erythema occurred in the antecubital fossae and on the sides of the neck.

Four days after the outbreak of the rash he had an eosinophilia of 768 per c.mm. The eosinophils were recorded as 416 per c.mm. 14 days later ; after a month the count had dropped to 204 per c.mm.

The local condition was treated with calamine lotion and he also was given "phenegan," one tablet three times a day. The treatment eased the irritation considerably, and gave him relief from the swelling of the eyelids. During the next week the skin condition subsided gradually.

Patch Tests

Patch tests were performed upon nine of the 10 people who had worked upon the process and had suffered from skin trouble. Tests were made with methylchlorosulphonate and with the ester (methyloctylbenzenesulphonate) as these substances were considered to be the most likely cause of the dermatitis.

In the early stages only crude preparations of the ester were available, and since both these and the methylchlorosulphonate were liable to cause primary irritation upon normal skins, a modified patch test technique was used.

Method.—Small squares of lint (1 cm. square) were soaked in the appropriate dilution of the substances tested. Excess liquid was squeezed out, and the gauze was then placed over the skin of the volar aspect of the forearm. The patch was held in position by a single strip of adhesive plaster and consequently dried rapidly following the evaporation of the solvent. Acetone was used as the vehicle for both substances in the initial tests. In the later tests the methylchlorosulphonate was dissolved in trichlorethylene. This precaution was taken to ensure that no destruction of the methylchlorosulphonate occurred by reaction with acetone. The results were read after 24 hours' contact.

Results.—Of the nine persons tested, eight gave well defined reactions to the ester in concentrations of 1%. No reaction was given to methylchlorosulphonate in the same concentration. Normal subjects did not react to this concentration of the ester, and in a few tests it was found that even the pure substance did not cause any reactions on the normal skin. The reactions produced by crude and pure samples of the ester did not vary appreciably in degree when both were diluted to one in a hundred.

The intensity of the reaction to the ester varied (as might be expected) in different subjects. The mildest reactions were manifested by a square of erythema at the site of the patch. The sites of the hair follicles were marked out by surrounding circles of deeper erythema suggesting some concentration of the material at these points (Fig. 2).

FIG. 2.—Patch test reactions (mild reaction) to 1% methyloctylbenzenesulphonate.

In the more violent reactions an intense uniform erythema was present and there was a "flare" on the surrounding skin. A variable amount of oedema and swelling of tissue in the immediate vicinity occurred.

Two of the subjects complained of mild eye symptoms 48 hours after the test.

No immediate reactions to methyloctylbenzenesulphonate could be elicited by the prick test technique.

Animal Experiments

A sample of the ester was applied to the clipped skin of six guinea-pigs. This caused no immediate reaction but after 72 hours a very faint erythema developed. Seven days later a second application of a 5% solution in acetone of the substance was given. This caused a violent erythema to develop after 24 hours, and the lesion developed over the following five days into a thickened, scaly lesion which subsequently faded.

Skin tests were carried out 14 days after the initial application. The test substances were applied to an area of depilated skin about 1 cm. in diameter by means of a glass rod. The following chemicals were applied :—

(1) Ester (methyloctylbenzenesulphonate): (a) 1% in acetone, (b) 0.1% in acetone. (2) Methylchlorosulphonate: (a) 1% in carbon tetrachloride, (b) 0.1% in carbon tetrachloride. (3) Quaternary salt (methyltriethylammoniumoctylbenzenesulphonate): (a) 1% in acetone, (b) 0.1% in acetone.

Positive reactions were obtained to tests 1 (a) and 1 (b) only. The reaction was manifested by an area of erythema which was of maximal intensity at 24 hours. In the more highly sensitive animals there was well defined oedema and thickening of the skin at the site of the application of the 1% solution. The reactions to 0.1% ester were similar but of less degree. Control animals gave no reaction to any of the test substances in the concentrations used.

Discussion

The evidence provided shows conclusively that the cause of the outbreak of skin trouble was the methyl ester of octylbenzenesulphonic acid. It is also clear that the ill-effects were due to the fact that this substance is a sensitizing agent. The fact that every person who had come into contact with the material experienced skin trouble and that eight of the nine subjects tested gave positive reactions to a patch test indicates that the material is of a high degree of potency. The reason for the failure of one of the subjects to react to the patch test is not clear. His initial symptoms were very mild and it is possible that he had become desensitized. An alternative explanation is that his initial symptoms were attributable to primary irritation and not to sensitization.

The nature of the clinical response to contact is similar to that reported among workers sensitized to tetryl (Schwartz and others, 1941). In these workers pricking of the eyes and swelling of the lids is noted as a common effect of exposure. This group of eye symptoms is not a common accompaniment of a skin reaction to locally applied drugs although it frequently accompanies a disseminated reaction to these agents.

Examination of the circulating eosinophils was possible in one patient only (Case 3). The high count was further slight evidence of the allergic nature of the reaction. It will be noted that "phenegan" apparently caused some improvement of this patient's subjective symptoms and relieved the swelling of the eyelids. There was no evidence that it modified the course of the skin condition.

The fact that guinea-pigs could be sensitized to this substance not only confirms the clinical findings, but provides a simple method of investigating the possibilities of cross-reactions. This technique has been used with advantage for the investigation of tetra sensitivity by Gell (1944). It is clear that neither the salt (methyltriethylammonium octylbenzenesulphonate) nor methylchlorosulphonate elicited the reaction.

Landsteiner (1945) propounded the general theory that simple chemical sensitizing agents became antigenic by virtue of the fact that they combined with proteins. This thesis was further substantiated by Gell (1944) and by Gell, Harington, and Rivers (1946). The ester, methyloctylbenzenesulphonate, would appear from its chemical nature to be capable of forming a compound with protein; linkage might possibly occur with an amino group of the protein via the SO_3 group, by the migration of the methyl group to the nitrogen of the protein amino group. It would form in effect a salt, the amino nitrogen carrying a positive charge, and the sulphonate group a negative charge. Further investigations concerning the mode of action of the compound are in progress.

It is appropriate to note that the outbreak which has been described occurred during the development phase of this particular process. Since this investigation the final plant, in which all of the processes are enclosed, has been installed. No further skin trouble has so far occurred.

Summary

An outbreak of dermatitis in a pilot plant for the production of an antistatic lubricant is described.

This was found to be due to the sensitizing properties of one of the intermediates, viz., methyloctylbenzenesulphonate.

The sensitizing properties of this compound were confirmed by skin tests on guinea-pigs.

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