ECZEMATOUS CROSS-HYPERSENSITIVITY TO AZODYES IN NYLON STOCKINGS AND TO PARAPHENYLENDIAMINE*

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In a preliminary report Dobkevitch and Baer (1) described cases of dermatitis on the feet, legs and thighs due to hypersensitivity to dyes in nylon stockings. In these cases hypersensitivity to paraphenylendiamine was present in addition to hypersensitivity to the stocking dyes. The regular, simultaneous occurrence of the hypersensitivity to the dyes in nylon stockings and to paraphenylendiamine suggested that there was a chemical basis for this cross-hypersensitivity. The present report discusses the chemical nature of the dyes tested and the reasons for the association of hypersensitivity to certain dyes and to paraphenylendiamine.

EXPERIMENTAL

The present series of cases comprises a total of 18 subjects, including, a) 13 subjects with stocking dermatitis and with no previous history of dermatitis due to dyes and, b) 5 subjects who had never had stocking dermatitis but who were known to have an eczematous hypersensitivity to paraphenylendiamine.

A. Tests in subjects with stocking dermatitis but with no known previous dermatitis due to dyes

In 13 subjects with dermatitis of the feet, legs, and/or thighs, nylon stockings were found to have been the cause of the eruption; strongly positive patch test reactions were produced in all these subjects with their own nylon stockings and/or nylon stockings which had been the cause of dermatitis in other subjects in this series. In order to find the cause of the dermatitis, patch tests were then carried out with materials used in the manufacture of the several brands of nylon stockings investigated. These materials included the unprocessed nylon fibers, dyes, "finishes", "softeners", "emulsifiers", etc.1 Tests with paraphenylendiamine also were carried out routinely, since the first two cases of nylon stocking

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1 Dr. Louis Schwartz was kind enough to obtain some of the test materials for us.
# Table I

*Dyes used for patch-testing*

<table>
<thead>
<tr>
<th>A.</th>
<th>CH₃CONHCHASE N≡N CH₃</th>
<th>(Color: yellow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.</td>
<td>CH₃CONHCHASE N≡N  Cl CH₃</td>
<td>(Color: yellow)</td>
</tr>
<tr>
<td>C.</td>
<td>O₃NCHASE N≡N CH₃</td>
<td>(Color: scarlet)</td>
</tr>
<tr>
<td>D.</td>
<td>O₃NCHASE N≡N CH₃</td>
<td>(Color: scarlet)</td>
</tr>
<tr>
<td>E.</td>
<td>H₂CHASE N≡N CH₃</td>
<td>(Color: yellow)</td>
</tr>
<tr>
<td>F.</td>
<td>CH₃CONHCHASE N≡N CH₃</td>
<td>(Color: yellow)</td>
</tr>
<tr>
<td>G.</td>
<td></td>
<td>(Color: yellow)</td>
</tr>
<tr>
<td>H.</td>
<td></td>
<td>(Color: violet)</td>
</tr>
</tbody>
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dermatitis in this series had shown a strong eczematous hypersensitivity to this compound, as evidenced by reactions to patch tests.

All tests were carried out with proper dilutions and in proper vehicles with adequate series of controls to rule out non-specific reactions and primary irritation.

The tests showed that all our subjects had a strong eczematous contact-type hypersensitivity to some of the dyes and to paraphenylenediamine, while there was no evidence of hypersensitivity to the other materials tested.

The color of the nylon stockings under discussion is produced by blending several dyes of different chemical constitution and color: yellow and red azodyes; yellow acridine and violet or blue anthraquinone dyes. The formulas and colors of the dyes tested are listed in Table I. In this table the dyes A, B, C, D, E and F are azodyes. Dyes G, H, I, J and K are anthraquinone and acridine dyes, unrelated to azodyes. Dye L, paraphenylenediamine, is a well-known dye for furs and human hair, but is not used in the manufacture of nylon stockings.
The results of the patch tests with two of the types of nylon stockings tested and with all the dyes tested are presented in Table II. Eleven stocking-hypersensitive subjects were also hypersensitive to paraphenylenediamine and to from three to six of the different azodyes tested. The remaining two stocking-hyper-

### TABLE II

**Patch test results in subjects with stocking dermatitis but with no history of previous dermatitis due to a dye**

| SUBJECT | NYLON STOCKING FROM PATIENT A. GO. | NYLON STOCKING FROM PATIENT S. R. | DYE L* (PARAPHENYLENDIAMINE) | DYE A* | DYE B* | DYE C* | DYE D* | DYE E* | DYE F* | DYE G* | DYE H* | DYE I* | DYE J* | DYE K* |
|---------|-----------------------------------|-----------------------------------|--------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| S. R.   | +++                              | +++                              | +++                             | +      | ++     | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| M. K.   | +                                | +                                | ±                               | +      | +      | +      | +      | +      | 0      | 0      | 0      | 0      |
| A. B.   | +++                              | +                                | +                               | +      | +      | ++     | +++    | ++     | 0      | 0      | 0      | 0      |
| B. N.   | +                                | ++                               | +++                             | +      | +      | ++     | +++    | ++     | 0      | 0      | 0      | 0      |
| C. I.   | +++                              | +++                              | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| F. H.   | +                                | +                                | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| H. F.   | +++                              | +                                | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| L. I.   | +++                              | +                                | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| S. R.   | +                                | +                                | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| A. G.   | +++                              | +                                | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| A. B.   | +                                | +                                | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| E. G.   | +++                              | +++                              | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |
| M. R.   | +++                              | ++                               | +++                             | +      | +      | +++    | +++    | +++    | 0      | 0      | 0      | 0      |

* For formula of dyes see Table I. Dye L was tested 2% in petrolatum; all other dyes were tested "as is."

— Indicates that material was not tested.

### TABLE III

**Patch test results in subjects known to be hypersensitive to paraphenylenediamine but with no evidence of stocking dermatitis**

| SUBJECT | NYLON STOCKING FROM PATIENT A. GO. | NYLON STOCKING FROM PATIENT S. R. | DYE L* (PARAPHENYLENDIAMINE) | DYE A* | DYE B* | DYE C* | DYE D* | DYE E* | DYE F* | DYE G* | DYE H* | DYE I* | DYE J* | DYE K* |
|---------|-----------------------------------|-----------------------------------|--------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| J. S.   | +++                              | +++                              | +++                             | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      |
| O. M.   | +++                              | +                                | +++                             | 0      | (+)    | +++    | 0      | +++    | 0      | 0      | 0      | 0      | 0      | 0      |
| A. Ge.  | +                                | +                                | +++                             | 0      | +      | +++    | ++     | +      | -      | 0      | 0      | 0      | 0      | 0      |
| R.      | ?                                | -                                | +++                             | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      |
| M.      | ±                                | -                                | +++                             | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      |

* For formulas of dyes see Table I. Dye L was tested 2% in yellow petrolatum; all other dyes were tested "as is."

— Indicates that material was not tested.

There were differences in the degree of reactions produced by the various dyes. From the patch test reactions elicited it appears that dyes A, B, C and F produced slightly weaker reactions than dyes D and E. Dyes A, B and F possess an acetylamino group. Dyes possessing such a group have long been known to have a relatively low sensitizing capacity among the azodyes.
ECZEMATOUS HYPERSENSITIVITY TO NYLON

B. Tests in subjects with known hypersensitivity to paraphenylenediamine but without stocking dermatitis

Because of the co-existence of hypersensitivity to azodyes and to paraphenylenediamine in our cases of nylon stocking dermatitis, five subjects with known eczematous hypersensitivity to paraphenylenediamine were patch-tested with the same materials used in the subjects with stocking dermatitis. None of these five subjects had a history or clinical evidence of stocking dermatitis. The results of these tests are presented in Table III. Three of the five subjects showed definite hypersensitivity to nylon stockings while in the two remaining subjects no such hypersensitivity was evident. In the only two subjects who underwent further tests with the stocking dyes, several of the azodyes elicited positive reactions while no reactions were produced with the dyes of anthraquinone- and acridine-type.

COMMENT

All the subjects suffering from nylon stocking dermatitis were hypersensitive to azodyes used in the manufacture of the stockings investigated and to paraphenylenediamine; but none of these subjects was hypersensitive to the other dyes which had been used in the manufacture of the nylon stockings and which are derivatives of anthraquinone or acridine.

Conversely, three of the five subjects with known paraphenylenediamine-hypersensitivity, but with no stocking dermatitis, were also hypersensitive to the nylon stockings containing the allergenic dyes. In the two subjects in this group who were further tested with dyes, the reactions to the azodyes were not as strong as in the subjects with stocking dermatitis, indicating a greater degree of specificity of the hypersensitivity or lower degree of hypersensitivity than in the subjects with nylon stocking dermatitis.

The explanation of the cross hypersensitivity to the azodyes and to paraphenylenediamine is found in the work of R. L. Mayer (2, 3, 4, 5) who showed in 1928 that there is a common chemical basis for hypersensitivity to azodyes and to paraphenylenediamine, namely, hypersensitivity to compounds of quinone structure. He states that living cells and especially the cells of the skin oxidize paraphenylenediamine to quinonediiimine according to the following reaction:

\[
\begin{align*}
\text{Paraphenylenediamine} & \quad \xrightarrow{O_2} \quad \text{Quinonediiimine} \\
\end{align*}
\]

Azodyes, according to R. L. Mayer, are also transformed in the skin but here a more complicated chain reaction takes place: the azo-compounds are first
split into two amines by reduction of the azo-linkage. The constitution of the resulting amines depends on the constitution of the original azodyes. For example, in the case of aminoazobenzene, paraphenylendiamine and aniline are formed; in the case of dye B (see Table I) monoacetylparaphenylendiamine and meta-chloro-ortho-aminophenol etc. These split products then undergo further transformation, the resulting compound of course depending on the various side chains or substitutions; however all of these split products undergo oxidation and if their chemical constitution permits are converted into quinoneimines, quinonedimines, or their derivatives. An example of such a chain reaction is as follows:

\[
\begin{align*}
N &= N \\
\text{Aminoazobenzene} &\xrightarrow{+4H} \text{NH}_2 + \text{NH}_2 \\
\text{Aniline} &\xrightarrow{+O} \text{NHOH} \\
\text{Phenylhydroxylamine} &\xrightarrow{+O} \text{Quinonedimine}
\end{align*}
\]

According to R. L. Mayer (2, 3, 4, 5) the hypersensitivity to paraphenylendiamine does not in all cases cross over to all azodyes, not even necessarily to those which are converted into quinoneimines or quinonedimines; nor do all cases of hypersensitivity to the azodyes show cross-hypersensitivity to paraphenylendiamine. This is understandable if we consider the fact that many azodyes contain substituted aminogroups which in the skin are only slowly and gradually transformed into free reactive aminogroups. In view of these facts, the presence or absence of cross hypersensitivity may be based on quantitative rather than qualitative differences.

Again, in some cases the hypersensitivity is primarily directed toward substituted amines and only to a lesser degree toward the free compounds. These facts, according to R. L. Mayer, explain the considerable specificity of the cross-hypersensitivity which is observed in some cases and the lack of cross-hypersensitivity in other cases.

Dyes C and D would give paraphenylendiamine if the —NO\textsubscript{2} group were reduced to —NH\textsubscript{2} either before or after cleavage of the azo-linkage. Harrow (6) states that nitro compounds as a fairly general rule are converted to the corresponding
amino-compounds. It thus appears quite likely that, in the skin too, such a reduction actually takes place.

On the basis of these considerations, the findings in our subjects can be interpreted as follows:

Group A. Hypersensitivity to paraphenylendiamine and azodyes. Example: Our subjects with nylon stocking dermatitis. In these cases there is a relatively wide hypersensitivity to the whole group of unsubstituted and substituted amines, based on a hypersensitivity of the skin to quinonediimine and all other compounds of quinone structure.

Group B. Hypersensitivity to paraphenylendiamine but not to azodyes. Example: Our two subjects with paraphenylendiamine hypersensitivity but no hypersensitivity to the allergenic dyes in nylon stockings. In these cases it seems probable that the allergenic principle is specifically paraphenylendiamine itself rather than a substituted derivative which could also be produced from various azodyes. It appears improbable that the lack of cross-reaction could be explained by the assumption that the tissues are incapable of effecting the usual splitting of the azo-linkage.

Group C. Hypersensitivity to paraphenylendiamine and only to several but not all of the azodyes. Example: Our two subjects without stocking dermatitis but with paraphenylendiamine hypersensitivity and hypersensitivity to only some of the azodyes. These cases would form an intermediate group between groups A and B, with a lesser degree of specificity than group B and a higher degree of specificity than group A.

CONCLUSIONS

1. In a series of thirteen cases of allergic eczematous contact-type dermatitis due to nylon stockings, the azodyes used in these stockings were shown to have been the causal allergenic factors. In all thirteen cases there was cross-hypersensitivity to paraphenylendiamine.

2. In a series of five subjects with allergic eczematous contact-type hypersensitivity to paraphenylendiamine, but no dermatitis due to nylon stockings, there was cross-hypersensitivity to the azodyes in three subjects. In the two remaining subjects no such cross hypersensitivity could be demonstrated.

3. The cross-hypersensitivity to paraphenylendiamine and to the yellow and red azodyes used in nylon stockings is explained by the mechanisms described by R. L. Mayer, according to which paraphenylendiamine and azodyes are transformed, in the body, into the actual allergens, namely compounds of quinone structure, such as quinonediimine and others.

DISCUSSION

Dr. R. L. Mayer: When I first noticed that certain azodyes and paraphenylendiamine gave cross-reactions and consequently studied this phenomenon, nylon was still unknown; nevertheless, it was evident that this sensitization had a great practical and theoretical value.

The practical value is explained by the fact that the substances falling into this group
are in constant use. For example, a woman who is sensitive to nylon stockings will not be able to wear mink-dyed muskrat or seal-dyed rabbit; she will not be able to dye her hair brown or black, to wear yellow leather belts or gloves, or to do her own photo-developing. And conversely, a woman who becomes sensitive to hair dye will sooner or later encounter difficulty when she wears nylon stockings. This list could easily be increased, since aromatic amines and azodyes have a very wide use. One other practical point should be reinvestigated. Certain azodyes which belong to the group of butter yellow are widely used as certified dyes for food,—macaroni, butter, etc., and though they do not produce sensitizations and give negative patch tests in otherwise azodye sensitive patients, it is quite possible that after ingestion of these dyes, cross-sensitizations and manifestations are elicited. This problem is, in my opinion, important enough to warrant further study.

The theoretic phase of this study is very interesting, and I only want to call your attention to the fact that these quinones-diimones are not only the most powerful skin irritants, but they also produce atypical epithelial proliferations. The same mechanism which is responsible for the skin irritations is also responsible for the production of the so-called anilin cancer, as I have shown in a special study of this problem.

The action of these substances as sensitizers and especially, as producers of atypical epithelial proliferations leading to cancer, is best explained by the fact that they react with certain important proteins depleting the cells of vital constituents. This last point deserves special mention in view of the more recent theories of cancer.

DR. LOTRIS SCHWARTZ: I was very much interested in hearing Doctor Baer's paper because the Office of Dermatology, USPHS, assisted somewhat in getting materials with which he did his tests. At the same time we also did tests with the finishes and dyes used in the 1—2 particular brands of nylon stockings which Dr. Baer called to our attention. The dyes used belong to the azo group, but this is a very large group of dyes having different properties. The butter yellow is actually used as a fat dye, and is entirely different from the azo-dye used for dying nylon stockings or other synthetic fibers. Cellulose acetate and regenerated cellulose are also synthetic fibers and the same type of dyes are used on them as on the nylon. In dying ordinary fabrics, the dye usually enters into a chemical combination with the fabric and produces a uniform color throughout the pattern. Synthetic fabrics are composed of solid threads,—they have no cells which the dye can penetrate and with which to combine. Consequently the dyes used have to enter into the solid resin cylinder of thread and then are distributed throughout in the form of granules of the dye itself. Some of the dye also coats the thread. You can readily see that the dye in these resin fibers retains its chemical characteristics whereas it may not do so in the natural fabrics. When the dye is soaked out of the synthetic fabric by perspiration, it is the dye alone which goes on the skin, whereas in natural fabrics it is not the dye itself, but the changed dye. For these reasons the reactions that Dr. Baer and Dr. Mayer explain may take place. The particular types of azo-dyes can be taken out of the synthetic resins and deposited on the skin by the perspiration, and then the changes previously described by Doctor Mayer may take place.

DR. RUDOLF L. BAER: I want to thank the discussors, Dr. Mayer and Dr. Schwartz, for their comments. We have seen a number of cases of cross sensitization to clothing materials and particularly to rubber gloves. The important point is that just as in the "epidemic" of nylon stocking dermatitis before the war the nylon fiber itself is not the cause. In our series of cases the dyes were the cause and not the finish.

I was glad to see that recently new colors of nylon stockings have become fashionable. These new fashionable dark colors (brown, blue and black) I assume do not necessitate the use of the red and yellow azo-dyes which were the cause of the dermatitis in our cases. Let us hope then that the new fashions will solve this medical problem for all of us.

REFERENCES


