

SENSITIVITY TO HAIR DYES

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THE use of ortho-, meta-, and para-diamino benzenes and aminophenols in combination with polyhydroxybenzenes in hair and fur dyes dates back to 1885.¹ Although an increasing number of persons use this type of hair dye, it is interesting to note that during the past twenty years the frequency of reports of sensitization to hair dyes has decreased. Many reasons can be advanced for the reduced frequency of sensitization. For one thing, the public has become educated to the existence of allergic reactions and consequently fewer persons with hair dye eruptions seek the aid of the physician. Furthermore, many women have learned of their hypersensitivity to particular dyes and after a first mild attack of dermatitis, or after a positive patch test, they avoid further exposures. The routine use of the patch test previous to the dying of the hair has become especially important. An additional factor is undoubtedly the greater purity of the chemicals used for hair dying. The importance of purification has been demonstrated by Sulzberger and associates,² who observed that purification of the dyes used in lipsticks reduced the number of allergic responses. Manufacturers have learned empirically to avoid the use of certain highly allergenic substances which produce natural hair color, and this also has reduced the number of allergic reactions. These facts suggest a revision of the problem and suggest that some of the older reports on this subject should be re-evaluated. Clinical reports which deal with pathologic changes that arise weeks or months after the last dye application should be discounted, if the symptoms reported do not conform with those observed under controlled conditions or in animal experiments with the compounds.

It may be emphasized that paraphenylenediamine and paratoluylenediamine do not penetrate the normal skin of man,³ or mouse.⁴ In fact, Sidi⁵ found that only seven persons were sensitive to paratoluylenediamine among twenty persons sensitive to paraphenylenediamine. To obtain a similar number of sensitizations, as with 2 per cent paraphenylenediamine, a 5 per cent paratoluylenediamine was necessary.⁶ Sulzberger and Rostenberg⁷ tested 411 subjects suffering from dermatoses or having allergic skin diseases with a 2 per cent paraphenylenediamine in petrolatum in a closed patch test and obtained 6.3 per cent positive reactions. In 1930 the incidence of sensitivity to hair dyes was reported to be 1 in 20,000 to 30,000, while in 1952 an incidence of one case of dermatitis for about every 80,000 packages of hair dyes sold was recorded according to

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Schwartz and Barban.⁸ No sensitivity was observed by them in testing 1,000 persons with various shades of hair dyes. Schwartz^{8, 10} attributed the drop in incidence to (1) increased use of the preliminary patch test, (2) purity of the components, and (3) greater care in preparing oxidizing solutions. However, Peck⁹ disagreed with Schwartz's findings.

At the outset, we wish to emphasize that the experimental conditions of the tests we are here reporting, as well as the composition of the clinical material, were somewhat different from those of previous investigators.

COMPOSITION OF HAIR DYES AND THE MECHANISM OF THEIR ACTIONS

Hair dyes contain not only paraphenylenediamine. In some, paraphenylenediamine is replaced by paratoluylenediamine, which is considered less toxic. Commercial hair dyes are combinations of various compounds. These compounds in varying concentrations are dissolved in a base consisting of soap, detergent, fatty alcohols, glycols, glycerine, alcohol, free and bound ammonia, and perfume. The total content of these compounds in the dye varies from 20 to 50 per cent. The highest concentration of aromatic amines is present in the dark shades (especially in the black hair dye). In use, the dye solution is mixed with an equal volume of 6 per cent H_2O_2 , or with solid urea peroxide. Pure aromatic diamines and polyhydroxy compounds are colorless and darken on oxidation. The alkaline peroxide mixture oxidizes the aromatic constituents of the dye and simultaneously bleaches the hair, thereby rendering it more receptive to the dyes. The dye components of low molecular weight penetrate the hair shaft, and are oxidized within the cortex to insoluble pigments. The pigments produced by oxidation with hydrogen peroxide are azines and oxazines bound to the protein of the hair.¹¹ Cross sections of the dyed hair show that the pigments are deposited in the cortex and not in the cuticle. The color produced by artificial deposition of pigment granules in hair and fur has the same natural appearance as that of the normal hair, which owes its color to melanin pigment deposition. Several authors believe quinone-diimine to be the first substance produced by the oxidation of para-hair dyes. This substance is highly irritating and sensitizing, has a characteristic odor, and is supposed to be the actual cause of the dermatitic reaction. Quinone-diimine is formed on oxidation of para-diamines in neutral solutions and in the absence of water. In the presence of water, this compound is rapidly decomposed. The presence of quinone-diimine has not been proved, nor has it been identified by its reactions or odor in the aqueous alkaline solutions of hair dyes after addition of peroxide.

Investigations by Cox¹¹ on the mechanism of oxidation of diamines have shown the presence of the Bandrowski base in the dye solution and on the keratin fiber. The actual coloring matter, the insoluble azine, was present inside the cortex combined with the protein and on the surface of the hair, but was not found in the dye solution. Contact with hair keratin, therefore, seems to be essential for azine formation. An aqueous solution or suspension of the Bandrowski base in the presence of peroxide does not penetrate the fibers and therefore cannot dye hair. For the dying process it is necessary that aromatic amines

penetrate the hair shaft and be oxidized therein. After dying fur with paraphenylenediamine and peroxide at an alkaline pH, the azine inside the dyed hair represented 27 per cent and the azine on the surface of the hair only 1 per cent of the diamine used. The Bandrowski base on the fur and in the solution or in suspension was equivalent to 45.1 per cent of the diamine. The unoxidized material, ammonia, and other reaction products accounted for the residual diamine. The azine and Bandrowski base formed on the surface of the fiber were easily removed by washing with soap and water. An excess of H_2O_2 did not improve dying, but caused the formation of more azine on the surface of the fiber. The azine formed contained, according to Cox, at least nine benzene rings. It was not extractable from the hair by pyridine or other solvents, and could be isolated only by dissolving the hair keratin in strong alkali. It did not melt below or at $300^\circ C$. An exazine of similar properties and structure was obtained after dying fur with para-aminophenol and peroxide at an alkaline pH.

PRESENT INVESTIGATIONS

The disparity between the assumed hazards of sensitization and the steadily increasing use of these dyes induced us to re-investigate the incidence of sensitivity. According to information received from one manufacturer of hair dyes used by hairdressers, one complaint was reported for approximately every 100,000 packages sold. From the description of symptoms, some claims appeared to be due to neither sensitization nor toxicity, but were nuisance claims. Clarification of this basic problem would benefit the dermatologist who usually is consulted only after allergies have developed.

MATERIAL AND METHODS

Patch tests were performed on 1,024 hospitalized patients who were free from any skin disorders and without history of allergic disease. As far as could be ascertained, none of the patients tested had previously used hair dyes. The persons tested were patients with tuberculosis, rheumatism, arthritis, and cardiovascular and neurological diseases—a very different group from that of Sulzberger and Rostenberg.⁷ For the patch tests hair dyes used by hairdressers were utilized—again a material completely different from that used by Sulzberger and Rostenberg. To obtain the greatest possible response, the black dye was chosen since it has the highest concentration of aromatic amine. Every person was patch-tested with the following three solutions, each mixed with an equal part of 6 per cent H_2O_2 :

- Solution A: Black hair dye which contained paraphenylenediamine as the main ingredient.
- Solution B: Black hair dye, which contained paratoluylenediamine as the main ingredient.
- Solution C: Control consisting of the hair dye base and containing the same concentration of soaps, detergents, solvents, free ammonia, resorcinol, etc., but no aromatic amines.

Hair dyes A and B contained 2.2 per cent and 3.2 per cent of the paradiamines, and a total concentration of aromatic amines and related compounds of approximately 5 per cent. For the tests, only fresh bottles of dye, filled to the top and freshly mixed with hydrogen peroxide, were used within ten to fifteen minutes after mixing. The mixture was applied with a cotton applicator to the skin, which had been previously cleaned with benzene, and the test area was left uncovered to simulate the actual conditions of use (open patch test). The dye-peroxide mixtures were applied to the right and left antecubital folds, respectively, and the control solution was applied to the right retroauricular region. Patients were instructed not to wash the test area for at least twenty-four hours. The test areas were inspected after twenty-four and forty-eight hours and again after one week. Erythema alone was considered a 1 to 2 plus reaction, the formation of papules was scored 3 plus, and the formation of vesicles was considered a 4 plus reaction. The results are summarized in Table I.

TABLE I. SEX AND AGE DISTRIBUTION

AGE (YEARS)	MALE	FEMALE	A TOTAL	REMARKS
14 to 20	7	34	41	
21 to 30	35	77	112	One female positive to A
31 to 40	87	95	182	
41 to 50	98	83	181	
51 to 60	93	72	165	Two females positive to A One female positive to B One male positive to A One male positive to B
61 to 70	40	56	96	One female positive to A and B One female positive to B
71 and up	61	144	205	
No age given		46	46	
	421	607	1,028	

In a number of cases, including all those which gave a positive reaction to hair dyes, the tests were repeated two to four weeks later and in some instances were carried out a third time, two to three weeks subsequently (Table II). To determine the incidence of cross sensitization, four persons sensitive to hair dyes were tested with 2 per cent aqueous procaine solution (Table III).

TABLE II. REPEATS

AGE (YEARS)	REPEATED		REMARKS
	ONCE	TWICE	
15 to 20	12	6	
21 to 30	46	20	Includes 1 positive case
31 to 40	43	22	
41 to 50	22	11	
51 to 60	35	7	Includes 4 positive cases
61 to 70	42	1	Includes 1 positive case
71 and up	101	--	Includes 2 positive cases
Total	301	67	Includes 8 positive cases

RESULTS AND DISCUSSION

The studies performed on 1,024 persons affirm the practical value of patch testing. The data are summarized in Table I, which gives the incidence of persons allergic to hair dyes in relation to age and sex. Our findings indicate that

sensitivity to the two different hair dyes is highly specific. Three of the 1,028 persons (0.29 per cent) were sensitive to paratoluylenediamine type dye, four (0.39 per cent) to paraphenylenediamine type dye, and one (0.10 per cent) to both dyes. No persons reacted to the control solution. Three of the sensitive persons were male and five were female. All eight denied the previous use of hair dyes.

It should be made clear that the dye solution, the soap, and other components have a micellar structure, the single micelles consisting of 150 to 300 fatty acid or detergent molecules. The aromatic amines at alkaline pH are more soluble in the soap detergent micelle than in the aqueous solution; consequently, the physicochemical structure of the base acts as a deterrent to sensitization because the enmeshing properties of the micelles diminish the actual amount of diamines in contact with the skin even after drying. In addition to the previously mentioned explanations, the composition of the base of hair dyes may also be a factor in a lesser incidence of allergic responses to hair dyes. At present, the base contains 25 to 40 per cent soaps, detergents, solvents, humectants, etc. In former years 80 to 90 per cent of the dye base was water.

TABLE III. SENSITIVITY TO PROCAINE

CASE	AGE	PROCAINE
Female sensitive to A	28	Negative
Female sensitive to A	55	Positive
Male sensitive to B	65	Positive
Female sensitive to A and B	78	Negative

The number of persons sensitive to the black hair dyes seems also to be related to age. Only one of the 516 subjects less than 50 years of age (0.2 per cent) was positive to the black hair dye containing paraphenylenediamine. The remaining seven persons found sensitive were in the age group of 51 years or older. The conspicuous difference in sensitivity to hair dyes in persons over and under 50 years of age was unexpected since, as a rule, sensitization is supposed to be less common after the age of 50. According to Kern,¹² the skin shows diminishing reactivity to test materials with advancing age. Our results would indicate the contrary. Since the tested persons had disclaimed previous use of hair dyes, the positive reactions might be due to cross-sensitivity to related compounds. It is well known that persons allergic to local anesthetics of the procaine group or to sulfonamides or antihistamines or azo dyes, including Food, Drug, and Cosmetic certified dyes,¹³ may be sensitive to paraphenylenediamine. Our own tests with procaine (Table III) on four subjects sensitive to the black hair dyes seem to confirm these findings. Of four persons allergic to black hair dyes, two gave a positive reaction to procaine (cross-sensitization to para-amino-benzene group). The patch test, therefore, has important practical implications and is essential for every person who contemplates hair dyeing. It will help to eliminate persons cross-sensitized to aromatic amines or polyhydroxy aromatic compounds, by various drugs, azo dyes, or other compounds and thus further reduce the incidence of dermatitis due to hair dyes. Patch tests should also be made by the hairdressers before each dye application.

While we, ourselves, have not observed development of an allergic reaction upon repeated patch testing with para-dyes, this possibility, as well as cross-sensitization, should always be considered. The educational literature should stress the fact that even the slightest erythema may represent acquired sensitivity. Persons with injured or inflamed skin should not use hair dyes. Thorough shampooing of the hair after dyeing is of great importance. It removes from the surface of the hair and scalp all unoxidized dye or oxidation products which are capable of producing allergy. The dye pigment itself is inert and is lodged within the hair. Opinions regarding the persistence of permanency of sensitization are not uniform, although most dermatologists regard it as permanent.

The importance of the consistency of the reactions to patch test in relation to medicolegal problems and in workmen's compensation cases was pointed out by Witten and Shair.¹⁴ In their carefully conducted experiment, they demonstrated that the standard patch test repeatedly performed is a highly reliable method for testing allergic contact type hypersensitivity and that consistent results are obtained on repetition. Our own interest was stimulated by an unpublished report by Sulzberger and Baer, who tested inmates of a penal institution with poison ivy extract. Several months later the same group was retested with the same extract and some of the previously strongly-reacting persons showed a decidedly diminished response. In our repeated patch tests (Table II), none of the persons found previously negative became sensitized on repetition. The repetitions of the patch test on the eight positive reactors gave the same response. In two, the reaction increased from 1 to 2 plus. In a third person, 28 years old, the patch tests were repeated twice, after one and five months, and showed gradually weaker reactions as compared to the first strongly positive test. A year later the same patient was retested with the same hair dyes three times at weekly intervals, and in all instances the patch test was negative. This is an exception to the rule that repeated exposures to a specific allergen in a sensitive person tend to increase rather than decrease the degree of reaction. However, graded dilutions of an allergen on repeated testing may show variations. Since standard concentrations have been used in our investigations, the consistency of our results is even more convincing in the light of Witten and Shair's work.

SUMMARY

Patch tests with oxidation (para-) hair dyes were made on 1,024 hospitalized male and female patients. Black hair dyes having the highest concentration of aromatic diamines were used. Two black hair dyes, one based on paraphenylenediamine and the other on paratoluylenediamine, were selected. Controls with the dye base which contained soaps, detergents, ammonia, resorcinol, and solvents were consistently negative. So far as could be ascertained, none of the persons, especially those found sensitive to the dyes, had used hair dyes previously. Of the eight persons found sensitive, three (0.29 per cent) reacted only to the black hair dye based on paraphenylenediamine, four (0.39 per cent) reacted only to the black hair dye containing paratoluylenediamine, and one

(0.10 per cent) reacted to both dyes. Age seemed to be related to incidence of sensitization. Only one person of the 516 patients 50 years old or younger was found to be sensitive to the paraphenylenediamine hair dye.

The remaining seven reactors were over 50 years of age and their positive skin tests with hair dyes might have been due to cross-sensitization to related compounds. In our experiments, two of four sensitive persons tested gave positive skin reactions with 2 per cent aqueous procaine solution. The patch test is essential, therefore, to any person contemplating hair dyeing.

The erythema in the positive cases was evident twenty-four hours after the application of the test solution, and in no instance was an increased or delayed reaction observed after forty-eight hours. The skin tests were repeated at intervals of from three to four weeks, once on 301 persons and twice on sixty-seven persons, including the eight sensitive persons. No change developed in the specificity of the reaction of persons sensitive to one or the other type of hair dye and no positive reaction appeared in previously negative cases. In the only patient under 50 years of age who was found to be sensitive to the dye, early repetition of the tests gave weaker reactions and repetition on three occasions a year later gave negative results.

The chemical composition of the presently used hair dyes, as well as the mechanism of the conversion of the para compounds into hair coloring pigments, is discussed.

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