

A LOOK AT PARA-PHENYLENEDIAMINE

Para-phenylenediamine is an oxidative substance that was initially formulated for use in dye at the end of the 19th century.

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comes and their central role in disease pathology and treatment, education of the patient may begin even before the diagnostic patch test is performed.

Important aspects of patient counseling include explaining the nature of their disease, for example, the delayed presentation of ACD [aka the importance of a delayed read at 96 hours]; the relationship with the immune system (sensitization to a chemical followed by elicitation of dermatitis with re-exposure) and the indifference to time (a substance the patient has been using regularly, briefly or intermittently can sensitize at any point). In certain cases, the topics of irritant contact dermatitis (ICD) and contact urticaria (CU) are also explained. Of note, unlike ACD, history rather than patch testing can often lead to the correct diagnosis of ICD and CU.

ICD, the most prevalent form of contact dermatitis, can at times precede or be a concomitant diagnosis with ACD.^{4,5} Unlike ACD, ICD may occur on the first exposure to an irritating or abrasive substance. The innate immune system is activated and inflammation ensues. CU (wheal and flare reaction), on the other hand, represents the least prevalent form of the ACD. It is an immune-mediated phenomenon governed by a hallmark IgE and mast cell-mediated immediate-type hypersensitivity reaction. We acknowledge this form of hypersensitivity due to its potentially deadly associated anaphylactic reactions and direct the reader to key sources.⁶⁻⁸

In this article, we highlight ACD and explore the top relevant allergens, regional and topic based dermatitis presentations and clinical tips and pearls for diagnosis and treatment.



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Allergic contact dermatitis (ACD) affects over 14.5 million Americans each year, notably defining itself as an important widespread disease.¹ Due to overwhelming patient morbidity, loss of school and work time and significant expenditures for healthcare visits and medications, ACD

represents a high economic burden. Fortunately, through keen patient interviewing and patch testing, an avoidable culprit may be identified. Remission can then occur with implementation of an allergen avoidance regimen. Education becomes the critical bridging intervention to ensure treatment adherence and symptom resolution. Patients who are unable to comply with avoidance regimens are at risk for sustained, recurrent, progressive or even systemic dermatitis.^{2,3} To ensure patients have an appropriate understanding of all the potential out-

A HISTORICAL PERSPECTIVE ON PARA-PHENYLENEDIAMINE

“No, you must keep your good looks. We live in an age that reads too much to be wise, and that thinks too much to be beautiful. We cannot spare you.”

The deleterious emphasis on youth and beauty is no more evident than in the moral fantasy of *The Picture of Dorian Gray* by Oscar Wilde. Originally published in 1890, the novel focuses on Dorian Gray, a fetching and affluent Englishman who receives perpetual youth at the expense of his soul. As his deeds and soul grow evil and ugly, he remains beautiful until his ultimate demise parodied by the destruction of a self-portrait.

The novel was not an instant classic, and was actually used as evidence against Wilde in a trial in 1895. Nevertheless, it remains a hallmark of English literature. Wilde had a personal love for beauty reflected both in his personal life and his literary works. To maintain his own youthful looks, it is reported that Wilde frequently dyed his graying locks.

Interestingly, it was also reported that he suffered from odd ailments such as pus-filled ear infections and an unidentified skin disease. His face, arms, chest and back would erupt with severe itching flares. Per history and described presentation, keen dermatology experts have suggested that Wilde experienced ACD.¹⁰ Given the practices of the times, experts believe that his condition was quite possibly related to his hair dyeing practices utilizing a derivative of the highly sensitizing agent, para-phenylenediamine (PPD). The hair dye could have easily transferred from Wilde's hands and hair to his ears, arms, chest and back leading to a recurrent ACD. In his attempt to seek youth and beauty, Wilde befell to experiencing an unsightly dermatitis.

Setting historical theories aside, PPD is a widely used culprit behind millions of reported and unreported cases of ACD. PPD is an oxidative substance that was initially formulated for use in dye at the end of the 19th century.¹¹ The main principle behind this ingredient was that when placed on hair and oxidized, it turned the hair black.

Large commercial hair dye promotion began in 1907 by Eugene Schueller, a

young French chemist. Safety experiments were not standard procedure and, it has also been reported that Schueller, an eccentric scientist, preferred to taste his chemical concoctions as a screening test for correct composition. Schueller's permanent hair dye product was named “Aureole,” which stood for “radiance around the head.”

Taking advantage of the new capital, Schueller opened his first company quite notably named “Societe Francaise de Teintures Inoffensives pour Cheveux” or “French Harmless Hair Dye Company.” The company name was eventually changed to the “non-sensical” name, L'Oréal, because Schueller liked the way it sounded.¹² L'Oréal has since become a leading cosmetic corporation worldwide.

PPD CHEMISTRY AND SENSITIZATION

To achieve the black color, PPD must be combined with a secondary ingredient, either a developer or oxidizer. Notably, PPD is then oxidized to the allergenic hapten either in the epidermis or the dermis.¹³ Of interest, PPD is most dangerous when it is in an intermediate state, partially oxidized and thus confers a higher occupational risk to hairdressers who handle the chemical throughout its composition. In the partially oxidized state, it also has greater capacity to cause allergy in sensitive individuals. A noteworthy clinical pearl is the observation that cross-reactions can occur between PPD and other com-

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pounds that also have an amino group in the *para* position of their benzene ring (**Table 1**).¹⁴

Cutaneous reactions to PPD vary but can range from a mild dermatitis of the scalp, upper eyelids (a thinner skin and thus, more sensitive to sensitizing agents) and the rims of the ears to severe blistering of the scalp with facial edema.^{15,16} In very rare, severe cases,

TABLE 1. CHEMICALS THAT CROSS-REACT WITH PPD¹⁴

Sunscreens with para-aminobenzoic acid
Sulfonamides
Sulphonylureas
Azo dyes in clothing
Local ester anesthetics (benzocaine, tetracaine)
Para-aminobenzene
Para-toluenediamine sulphate
PPD, para-phenylenediamine.

urticarial-type reactions with anaphylaxis have been reported.¹⁵

Recently, Haluk et al reported a 15 year-old adolescent female who had been unaware of being previously sensitized to PPD from a black henna tattoo who developed an angioedema-like reaction after her first exposure to hair dye.¹⁷

USAGE AND REGULATIONS

In the early 1930s, the practice of tinting eyelashes and eyebrows with PPD-infused dyes was common. “Lash Lure,” a popular tinting product, was reportedly associated with serious reactions including blistering, blindness and even death. These incidents led to the revision of the obsolete Food and Drugs Act of 1906 and development of the Food, Drug, and Cosmetic Act of 1938, which extended regulatory control over cosmetics for the first time.¹⁸ Under this new law, the first regulatory

action implemented was to remove Lash Lure from the consumer market. Furthermore, the use of PPD in cosmetics directly applied to the skin became prohibited (although quite notably the application of PPD in hair dye was exempted).^{19,20}

In 1939, in the first published standard series of patch test antigens, Bonnevie suggested PPD be used for the diagnos-

Table 2. EXAMPLES OF PTDS-BASED ALTERNATIVES TO PPD-BASED HAIR DYE.⁴²

PTDS-Based Permanent Hair Dye Products	Goldwell Color Chic
	Schwarzkopf Igora Royal
	Wella Koleston Perfect
PTDS-Based Demi-Permanent Hair Dye Products	Clairel Professional Beautiful Collection Advanced Gray Solution
	Goldwell ReShade for Men
	L'Oréal Paris Excellence To-Go 10-Minute Crème
	Schwarzkopf Igora Viviance
	Sanotint Light
	Wella Color Charm Demi Permanent
<p><small>Notably, some individuals allergic to PPD may have cross-reacting allergies to PTDS due to their related chemistries. Therefore, allergic persons should utilize caution in introducing these new products. PPD, para-phenylenediamine; PTDS, para-toluenediamine sulfate.</small></p>	

tic screening of ACD to hair-dyes and furs.²¹ Also, for the last 80 years, PPD has remained one of the most prevalent allergens and atop most standard series panels. In 2006, PPD was designated by the European Commission and Scientific Committee on Consumer Products as 1 of the top 10 strong sensitizers,²² and with the prevalence of contact sensitization on the rise in North America, it was designated the Allergen of the Year by the American Contact Dermatitis Society (ACDS) that same year.²³

Because of PPDs ability to provide a natural look with permanent results,

result in severe dermatitis and long-lasting consequences such as scarring and post-inflammatory pigment changes (**Figure**). As previously mentioned, the use of black henna tattoo can sensitize patients to PPD-containing hair dyes.²⁶ The maximum permitted concentration in hair dye is 6%, however; studies show that the levels of PPD in henna tattoos are alarmingly higher — up to 29.5%.²⁷⁻²⁹

In response to increased reports of “temporary-water-application-tattoos” (notably many in children), the FDA has issued an advisory warning and created

PPD is most dangerous when it is in an intermediate state, partially oxidized and thus confers a higher occupational risk to hairdressers who handle the chemical throughout its composition.

it has remained the most popular permanent hair dye chemical. Despite the sensitization risk, more than 50% of female residents of developed countries worldwide use permanent or temporary hair dyes for some period of their life.²⁴ Hair dyeing is also becoming increasingly popular among the male population. Sensitization to PPD should be acknowledged as an occupational hazard for hairdressers and cosmetologists who may have daily exposures.²⁵

Although PPD use is allowed in hair dyes, the FDA prohibits its use on the skin.²⁰ In spite of this, many temporary tattoo artists mix PPD with “natural” henna to give it a brown-black color and to accelerate the fixing time of a temporary henna tattoo.²⁶ Its use can

a reporting hotline: MedWatch, 1-800-332-1088.^{19,30-32}

Furthermore, the inherent mutagenic properties of PPD have been demonstrated in rats: female rats subjected to topical application and subcutaneous injection of PPD had increased incidence of mammary, uterine and soft tissue tumors.³³

PRACTICALS OF PATCH TESTING

Patch testing is often necessary to identify the relevant allergen(s) responsible for the patients’ ACD. Screening patch test trays are available to isolate the most common chemicals and offer the clinician clues for potential sources. The ACDS North American Standard Series includes allergens from several different



Figure 2. Some temporary tattoos can cause severe dermatitis and long-lasting consequences.

categories.³⁴ Supplemental trays (such as hairdressing, dental materials, cosmetics and fragrance/flavors) are also available for purchase.³⁵

Furthermore, many cosmetic products can be tested “as is,” as is often recommended on the instructions included with hair dye. The European Cosmetics Toiletry and Perfumery Association advises hair dye manufacturers to instruct its consumers to perform a self-allergy test prior to product use. However, instructions often vary even among products from the same company, and it is unclear how many consumers of the intended audience actually follow-through with the process.³⁶

PEARLS OF TREATMENT: EVERY DOSE COUNTS IN AVOIDANCE

A person might be exposed to and subsequently sensitized to a particular allergen for days to years before actually developing ACD. Exposures can be additive, eventually causing one’s immune system to become trained to identify a chemical, at which time a cutaneous response would be elicited upon exposure.⁴

Just as repeated contact over time leads to an immune response, repeated avoidance over time will induce remission. Avoidance creativity, however, may be necessary by utilizing alternatives and by being aware of indirect exposures. For example, PPD exposure can occur by “second hand,” as in “conjugal contact dermatitis.” Both spouse and children have been reported to have acquired ACD from exposure to close contacts who used hair dye with PPD.^{37,38} As this may easily be underrecognized and missed, underscoring the

importance of a detailed patient history including avocations and close contacts habits should be stressed.

Unfortunately, PPD is not a rare or selective additive as it is also present in black rubber, scuba gear, photographic developers, printing inks and textile and fur dyes.

There are programs available to aid in the avoidance endeavor. The Contact Allergen Management Program, a service offered through ACDS, and the Contact Allergen Replacement Database, developed by Mayo Clinic, can assist with identifying allergen-free products.^{39,40} Both programs allow the provider to personalize “shopping lists” of products devoid of specific dermatitis-inducing chemicals, as well as any cross-reactors. For example, **Table 2** lists manufacturers that have developed PPD-free hair dye alternatives based on para-toluenediamine sulfate (PTDS).⁴¹ Notably, some individuals allergic to PPD may have cross-reacting allergies to PTDS due to their related chemistries. Therefore, allergic persons should utilize caution in introducing these new products. ■

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