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THE ALLERGENICITY OF PARAPHENYLENDIAMINE. I

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Abstract. R. L. Mayer's theory, concerning the allergenic activity of the intermediary products of *p*-phenylendiamine, with special consideration of benzoquinone, is discussed.

The allergenicity of paraphenylendiamine (PPD) was first described by Mayer (6) who also summarized his findings in a later publication (7). His pioneering work led to the recognition of the allergenic importance of the para position, and especially of the significance of the structure of quinone. This has subsequently been verified in several reports on this group allergy, the literature on which is immense. In connection with cross reactivity with nitrobenzene and aniline, phenylhydroxylamine is believed to play a central role, although this has not been confirmed by Schwarz-Speck (13). When the allergenicity of PPD is analyzed the actual allergenic oxidation product concerned cannot be determined (9). PPD in watery solution, which is often used in patch testing, is unstable and the initial product is oxidized. This led to the introduction of the more stable vaseline vehicle for PPD patch tests such as was used, e.g., in the Scandinavian test series (5).

Mayer held the view that on complete oxidation, PPD is converted first into relatively unstable quinonimine(s) and quinonediimine(s) which form substances of quinhydrone character with the residual PPD), and then into the more stable yellow benzoquinone (*p*-benzoquinone). If there is incomplete oxidation, the so-called Bandrowski base (Fig. 1) is formed. According to Mayer the living cell rapidly oxidizes PPD to quinonediimine. Moreover, he considered that "the classical chemical oxidation of PPD leads ultimately to benzoquinone but it is not known if this relation also takes place in the animal body. It is possible that the black polymerization products which formed in and upon the living cells from PPD, contain quinone and PPD in addition to quinonediimine" (7).

These theoretical assumptions are based on skin tests made by Mayer on hypersensitive patients and guinea pigs. Without giving details in a summary table he states that if the PPD reaction is 4+, then quinonediimine reaction is 6+, Bandrowski's base reaction is 4+, and benzoquinone reaction is 2+.

His experimental findings concerning, for example, benzoquinone, do not agree with the theoretical assumption concerning the mentioned dominant role of this substance. Moreover, Sidi & Longuevilli (14) consider that the injurious effects of hair dye are due to the incomplete oxidation of PPD, resulting in Bandrowski's base, and they recommend as treatment an accelerated oxidation by rinsing with "oxygenated" water.

With regard to *p*-quinonimine (which Mayer produced according to the method of Willstaedter & Pfannenstiel (16), the majority opinion in the chemical literature is that it "is extremely sensitive and has been isolated and characterized potentiometrically only by special techniques; even in an oxidation conducted at 0° in dilute acid solution, it is only a transient intermediate and undergoes hydrolysis to quinone. PPD similarly is converted into quinone through the easily hydrolyzed intermediate *P*-quinonediimine" (3). Because of the instability of these products, which are not available commercially (4), their use is extremely problematical when appropriately diluted as characteristic original substances in sensitization studies and tests.

In a study of sensitization of plants and tropical tree species, Schulz et al. (12) found that the allergenic factor was of a quinoid chararter. They

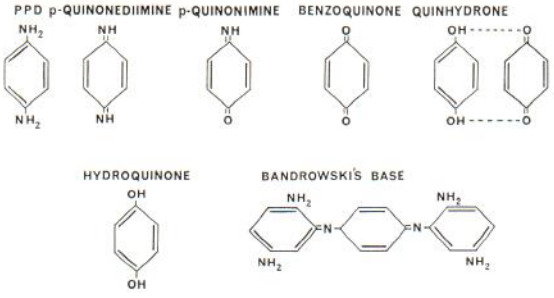

Fig. 1. Formulas of mentioned substances.

point out that the allergen of Primula Obconica, Primin, whose chemical structure has recently been elucidated (11), consists of a benzoquinone nucleus with an aliphatic side chain and a methoxy group. The significance of benzoquinone in connection with PPD-allergenicity can be discussed on the basis of the following experiments conducted by the authors: PPD, air-oxidized in presence of water, in vitro, was investigated by paper-chromatography (1) parallel with benzoquinone. As far as we know, many hitherto incompletely known spots were obtained from the oxidized PPD. Some of the spots were extremely sensitive to air and rapidly changed colour. Thus, for example, an intermediate zone turned blue within seconds. The same behaviour as regards colour change was also observed with a freshly prepared water solution of quinhydrone. The actual zones were compared photometrically: the spectra were partly identical with hydroiodic acid iodine which was liberated (17). Carven's reagent (2), however, reacted atypically for the actual zones and also for unseparated, oxidized PPD. In further experiments, small amounts of benzoquinone added to oxidized PPD were not with certainty detectable by Carven's reagent. Our in vitro experiments hitherto have shown that benzoquinone, if present, exists only in traces in air-oxidized PPD. The complete transformation of PPD in vivo is still unknown (15), although, on the other hand, Medola & Evans, described in 1891 how PPD at room temperature formed considerable quantities of benzoquinone in the presence of a strong oxidizer ($K_2Cr_2O_7$). (II) Patch tests were made on 5 patients, highly hypersensitive to PPD, by means of the paper chromatographic method previously described by the authors (1). The result indicated that the strongest reaction was most likely caused by the benzoquinone-containing spot.

The present investigators feel it is still an open question which of the quinoid substances must mainly be regarded as the active allergen in PPD-sensitization. The analogy is the question of the actual allergen in connection with chromium or turpentine. It follows that, in this respect, benzoquinone seems to be especially active. We have studied, by means of further experiments on guinea pigs, the problem of allergenicity in connection with PPD, which is the subject of another publication (10).

REFERENCES

1. Blohm, S. G. & Rajka, G.: Acta Dermatovener (Stockholm) *46:* 432, 1966.
2. Carven, R. J.: Chem Soc (London) 1605, 1931.
3. Fieser, F. & Fieser, M.: Organic Chemistry, p. 757. C. G. Harrap & Co., London, 1953.
4. Handbook of Chemistry and Physics. 43 ed., Chemical Rubber Publ. Co., Cleveland, 1961/1962.
5. Magnusson, B., Blohm, S. G., Fregert, S., Hjorth, N., Høvding, G., Pirilä, V. & Skog, E.: Acta Dermatovener (Stockholm) *46:* 153, 1966.
6. Mayer, R. L.: Arch Derm Syph *156:* 331, 1928.
7. — Group sensitization in compounds of quinone structure and its biochemical basis. Role of these substances in cancer. Progr Allergy 4, pp. 79–172. S. Karger, Basel and New York, 1954.
8. Medola & Evans, quoted by Meyer, H.: Analyse und Konstitutionsermittlungen organische Verbindungen. Springer, 1916.
9. Modée, J. & Skog, E.: Acta Dermatovener (Stockholm) *42:* 280, 1962.
10. Rajka, G. & Blohm, S. G.: Acta Dermatovener (Stockholm). In press.
11. Schildknecht, H.: Angew Chemie 76, p. 177. Beilage, 1964.
12. Schulz, K. H., Schmidt, P. & Grell, H.: XIII Congr. intern. Derm., München, 1967, vol. II, p. 1531. Springer, Berlin, 1968.
13. Schwarz-Speck, M. & Schwarz, K.: Int Arch Allergy *16:* 163, 1960.
14. Sidi, E. & Longueville, R.: Les accidents par produits capillaires. Flammarion, Paris, 1958.
15. Williams, T. R.: Detoxication Mechanisms. Chapman & Hall, London.
16. Willstaedter, R. & Pfannenstiehl, A.: Ber Dtsch Chem Ges *37:* 4605, 1904.
17. Vogel, A. I.: Practical Organic Chemistry. Longmans, Green & Co., 1956.

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