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THE ANILINE TEST AS DETECTOR OF A GROUP SENSITIVITY

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In 1936 Flandin and co-workers described a positive skin test to aniline in 4 patients who had previously shown a positive reaction to novocaine. But only in 1 of these 4 cases did paraphenylenediamine and paraminophenol give the same positive result. It seemed therefore that there might be a connection between the response to aniline and to other benzene derivatives with primary or tertiary amino groups (Baer 1948, Sidi et al. 1951).

Recently a patient gave a positive skin test to aniline and hydroquinone without giving a positive response to paraphenylenediamine. It was decided to make a basic study of the problem of the peculiar response to aniline. This it was considered might represent the response occurring at the same time as a sensitivity towards the para-amino substituents and the hydroxi-parasubstituents in the aromatic ring.

From a practical point of view, a positive aniline test was considered as indicating that the entire group of aniline dyes was responsible as a sensitizing agent. In some cases, it is possible to note this connection by considering the occupation, clothes, food and habits of the patient, but in other cases the problem cannot be solved in this way, because a positive response to aniline cannot be ascribed to any contact, while an allergy to sulpha drugs is known from the patient's history.

Serial patch tests have shown what, from a theoretical

standpoint was to be expected, that a positive aniline test¹ indicated a general hypersensitivity to the amino group (to compounds of quinone structure, cf Mayer 1948). So far among our cases there has been no exception to this rule. Moreover the reaction is the first to appear, it is always marked (there have never been any doubtful or slight reactions), and it should therefore always be used when investigating benzene derivative sensitivity.

According to our observations, the following series of hypersensitivities has been examined with regard to the order in which they usually appear and therefore to their practical importance during testing:—aniline¹, para aminophenol, hydroquinone, procaine, paraphenylenediamine², and, less important, sulpham drugs, paraminosalicylic and para aminobenzoic acids and their derivatives, antihistamine drugs, resorcinol, phenol, etc.

It may be possible that a contact with aniline dyes followed by sensitization, might enhance a general sensitivity to amino-groups. It happens, however, that many a candidate to a hypersensitivity to paraphenylenediamine for instance, begins with a positive response to an aniline patch test and with a clinical allergy to sulphonamide compounds. A patient in fact may become sensitized by either sulpham or antihistamine drugs or local anaesthetics. In all these cases, however, a cross-sensitization ensues and the first one to appear and the most obvious of the skin tests carried out with substances of this special group, happens to be that to aniline.

The method of patch testing with aniline has therefore simplified methods to detect hypersensitivity of a person to an entire group of substances. The saving of material, time and space on the patient's skin (often the dermatitis is widespread on the skin or many other tests have to be carried out) thus becomes considerable.

A sensitivity to the aniline amino-group carries the whole

¹ Anilin pro analysi Merck, 10 % in sweet almond oil.

² 2 % in white petrolatum.

problem of the sensitization to the so-called para-group back to its most elementary terms, thus greatly simplifying its interpretation. In the case of aniline, we have only to deal with one amino-group which is known to oxidize at a skin level into iminoquinone (Mayer). This substance reacts thereafter with the amino-acids and with the —SH groups of keratin. Now, it may happen that in some people the amino-group does not oxidize sufficiently, thus exposing the organism to its harmful action, or, as Mayer thinks, the harmful compound may consist in the iminoquinone itself or paraminophenol (Rajka 1952), which does not lend itself to further combination with proteins.

We are free to believe that the same thing happens in case of an allergy to —OH groups of phenol and diphenols, which is closely related with that to the amino-group. We call to the reader's attention the fact that —NH_2 , —CONH , as well as —OH , are typical polar groups and that is to say electrically active groups, which are more liable to combination. This makes them lose their harmful properties when they come into direct contact with the organism (e.g. diphenols tend to form phenolsulphuric ethers). But the aromatic compounds containing the —NH_2 or —OH groups in a para position, show, some more some less, a notable degree of apolarity as to the same groups when in ortho- or meta-position. This indicates that chemical affinities are not too evident when compounds are arranged in a para position and detoxifying combinations are not easily available in this case.

Besides, it is probable that also the polarity, and thus the tendency to the conjugation, of simple monosubstituents in the aromatic ring (aniline and phenol in this case) is inferior, owing to their lesser degree of asymmetry, as to that of compounds with double substitution in meta or ortho position, just as it was noticed in the pharmacological experiments with metaminophenol compared to those containing phenol.

Actually, we find that benzene rings, either with monosubstituents or with paradisubstituents, can hardly be blocked or detoxified at skin level.

How can we now conceive the relationship existing, from an allergologic point of view, between amino- and hydroxi-derivatives of benzene? Their mechanism in damaging the skin appears to be almost analogous; but does hypersensitivity always develop in a parallel and similar manner?

We believe that a person who, for instance, frequently comes into contact with hydroquinone, often, on patch-testing, shows a greater sensitivity to this compound than, e.g., to phenol. But we do not think there occurs what it usually seen among amino-derivatives, and that is that there ought to be, *at least while testing*, a primary sensitization to aniline which contains the simplest amino-group. Though the parallelism between the two groups of phenomena is not too probable, yet their simultaneous onset is very likely, although to prove it for certain, we should need a larger number of observations; much larger indeed than that which we have been able to sum up so far, as we do not usually encounter positive reactions to hydroxi-derivatives of benzene, which is so frequent in the U.S.A. and in Scandinavian countries.

We have made use of our observations on experimental facts in order to make clear our point of view on what, up to this date, was called an hypersensitivity to the "para"-group or to "quinone" structures, and which we propose to call a hypersensitivity to amino- and hydroxi-derivatives of the benzene ring, when these functions show a weak polarity.

SUMMARY

The aniline patch test represents a good method for detecting a possible hypersensitivity to aromatic compounds, whether amino- or hydroxi-derivatives, especially when in a para-position.

As a result of these observations the more usually used terminology may have to be changed. Instead of referring to

sensitization to the para-group or to quinone structure, one may refer to the more exact term and speak of sensitization to the amino- and hydroxi-group of the benzene ring when such groups are in a position of weak polarity.

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