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ON HYPERSENSITIVE TO "PARA GROUP"

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Allergy to paraphenylenediamine (PPD) has been known for some time because of the extensive use of this substance in the dye industry. On the basis of our observation of 918 patients we could demonstrate 3.0 % PPD hypersensitivity with the patch test method. The real importance however of PPD allergy is that we may give data to elucidate the connection between chemical structure and sensitization. It is not necessary to emphasize the theoretical and practical importance of that task, since it would offer a real basis for that difficult and important pathological problem only partially evaluated as yet. *Landsteiner* was the first to prove in his animal experiments that certain labile chemical groups, chains, the so-called determinants, acquire a decisive role in sensitization. The exact meaning of what we call determinant is open to discussion. It includes not only simple chemical groups as acid group or aliphatic side chain, but also positional and dimensional isomery and even isostery symbolising physiochemical resemblance (1).

The fact that compounds of para-, meta-, ortho-position proved to be different from the point of view of sensitization is a good example of positional isomery ("Stellungsisomerie"). This is extremely well demonstrated in *Landsteiner's* precipitation animal experiments made with p-m-o-aminobenzene-sulfonic acid (2).

Several authors point out however that the results of investigations with artificial sensitization do not entirely correspond to observations gathered on human spontaneous sensitivity. On the other hand it is quite difficult to collect data concerning the latter. From investigations in this field, chemical allergy of the "para group", the so-called "para group" hypersensitivity, is the one that is best known. As will be mentioned later, some work has already been done on it. The conclusion, drawn from results achieved so far, is also important for daily medical practice; namely there is good reason to believe that some of the commonly used drugs as the sulfonamides and procaine are not only good sensitizers themselves eliciting numerous symptoms of drug allergy, but they sensitize mutually each other and also to other compounds and drugs of similar chemical structure. Many allergic drug symptoms of doubtful origin can be explained in this way and these facts suggest the introduction of some contraindications which are recently under discussion.

We know since *R. L. Mayer's* basic experiments (3) that PPD and similar compounds such as aniline, p-amidophenol and so on or chemical agents transforming into them in vivo (e.g. azodyes) are converted to quinone structure compounds in the skin by oxydoreductive systems and these have a significant sensitizing power (4). In consequence it could be understood why two compounds e.g. PPD and a chemical agent of similar structure converted in the skin to quinones, will develop cross reactions. Sensitized to PPD, the patient will react with allergic symptoms, positive patch test to p-amino-benzoic esters (local anaesthetics: procaine, benzocaine etc.) latter, etc. (5).

Ever since the wide use of sulfonamides it has become obvious that sulmonamide compounds, PPD and even p-amino-benzoic esters (local anaesthetics: procaine, benzocaine etc.) give cross reactions too (5), that means, the same person may react positively to all the above mentioned compounds though being sensitized only by one of them. E.g. use of procaine on a sulfonamide allergic subject (e.g. at tooth extraction) may

provoke allergic symptoms. The intensity and variety of these symptoms will depend on the method and quantity of the procaine used, the "intensity" of hypersensitivity and other similar circumstances. The para-amino- is the common radical, the determinant group and new compounds in increasing numbers as p-aminobenzoic acid and glycerol p-aminobenzoate used as a sun-filtering agent, food-, drug-, cosmetic- and nylon stocking dyes are included in this group (5, 8). Recently cross reactions have been extended also to such compounds which have no amino group, e.g. trinitrophenol (picric acid) (9). This suggests that not even the presence of the amino group is absolutely necessary (10, 11) but it is quite permissible to use the expression and term "para group" hypersensitivity (12).

Widely differing types of hypersensitivity to the "para group" have been described (7, 13, 14). Below we summarize the results of patch tests carried out at our department on patients sensitized to "para group". Since it is a well known fact, that reading of results of patch reactions must be made with great care and many circumstances must be considered, in cases where the patch test reactions were not absolutely convincing we marked them as such and also made a distinction between the + ? and — ? signs indicating thus very limited differences too (see table I).

It will be seen from table I that all our patients belonged to subjects sensitized to "para group" (cases 9 and 12 see below). There may be a wide range of individual differences. All our 23 patients may be treated as *potentially* sensitized to "para group"; by that we wish to express that they may show hypersensitivity towards anyone of the compounds belonging to that group. We cannot predict however what kind of allergic spectra we have to face, to what types of "para group" compounds the patient will react positively. This can be determined only after examining all the compounds.

Separate sensitization with all the compounds must be assumed as a more theoretical possibility in cases of "para group" hypersensitivity, where we obtained positive reactions

with different "para group" compounds. The theoretical basis of cross reactions between "para group" compounds is proved by the findings that the preceding contact and therefore separate sensitization can often be excluded. The final reason for the fact that the individual "para group" hypersensitivity cannot be generally predicted is that the exact mechanism of sensitization is unknown. The supposed cause of individual differences on subjects sensitized to "para group" is that we don't know the way and mechanism of the transformations of chemical allergens in the organism. In certain cases it seems that the chemical allergen is apt to produce sensitization and elicit allergic reactions linked as a hapten to proteins (conjugated allergen), while in others differently linked from qualitative and quantitative points of view, this is not the case. It is possible as *Tzanck, Sidi and Morrill-Dobkevitch* (15) state—that the original sensitizer has also some determining effect on the allergic spectrum. They say e.g. that 55 % of the sulfonamide sensitive react to PPD and procaine too, on the other hand only 35 % of PPD allergic patients reacted to sulfonamide and procaine. We also observed PPD negative reactions in cases 18, 19 and 20 and two other unpublished ones who suffered from procaine dermatitis.

It would, however, not be reasonable to draw any definite conclusions from the data of table I though we mention some interesting ones. The fact that ortho-amidophenol (ursol II G) and other ortho-compounds did not give positive reactions emphasizes the importance of para structure; the same was proved by percaïne (nupercaine), which is not a p-amino-benzoic derivate in contrast to the other mentioned local anaesthetics. Some positive reactions noted with meta-compounds, which do not agree with the previous supposition are ascribed to the possibility that the applied meta-chemical, meta-phenylenediamine especially, was contaminated with slight traces of the para isomer and this was enough to elicit positive reactions on subjects sensitized to "para group".

Table II shows how numerous are the difficulties when dealing with chemical structure and sensitization and how in-

TABLE I

Paraphenylenediamine, HCl: ursol D
O-aminophenol: ursol II. G
P-amidophenol: ursol P base
Dimethylparaphenylenediamine: ursol DMG
Procaine: paraaminobenzoyldiethylaminoethanol
Percaïne: nupercaïne: alpha-butyloxycinehonincarbonic acid-diethylenediamide
Pontocaine: para-butylaminobenzoyldimethylaminoethanol
Benzocaine: paraaminobenzoic ethylester
Cycloform: paraaminobenzoic isobutylester
Sulfathiazole: paraaminobenzenesulfamidothiazole
Prontosil: sulfonamido-diaminoazobenzene
Paraaminosalicylic acid: PAS
Amaranth: 2-oxy-1,1'-azonaphthalene-3,7,4'-trisulfonic sodium
Bordeaux BL: 2-oxy-1,1'-azonaphthalene-3,7-disulfonic sodium
Neucoccin: 2-oxy-1,1'-azonaphthalene-6,8,4'-trisulfonic sodium
Orange I: 4-oxy-1-naphthalene-azobenzene-4'-sulfonic sodium
Acid yellow: mixture of 4-aminoazobenzene mono- and disulfonic sodium
Patent blue A: diethyldibenzyl-paraaminoxy-disulfofuchsonimonium Ca
Tartrazine: 1-parasulfophenyl-4-parasulfobenzeneazo-5-pyrazolone-4-carbonic sodium
Pellidol: diacetylaminoazotoluene
Methyl orange: paradimethylaminoazobenzene-parasulfonic acid
Nylon stocking: coloured with azodyes
Metol: para-methylaminophenol
Hydroquinone: para-dioxybenzene
Resorcinol: meta-dioxybenzene
Catechol: ortho-dioxybenzene: pyrocatechol
Pieric acid: 2,4,6-trinitrophenol
Pyrogallol: 1,2,3-trioxybenzene
Benzidine: para-para-diaminodiphenyl
Benzyl benzoate: benzoic benzylester
Ortho-nitranisol: ortho-nitrophenyl methylether

TABLE I

Cases No	1.	2.	3.	4.	5.	6.	7.	8.	9.
Paraphenylenediamine 2 %	+++	++	+	++	++	++	+	+	+
Paraphenylenediamine, HCl "	—	++	—	—	+++	+	—	—	—
O-amidophenol "	—	—	—	—	—	—	—	—	—
P-amidophenol "	—	—	—	++	++	—	—	—	—
Dimethylparaphenylenediamine. "	—	—	—	++	++	—	—	—	—
Procaine hydrochloride pdr	+	+	—	+++	—	++	—	++?	—
Procaine hydrochloride 1 %	— ¹	—	— ²	—	—	+	+	+++	—
Percaine (nupercaine) "	—	—	—	—	—	—	—	—	—
Pontocaine hydrochloride "	—	—	—	±	—	—	—	—	—
Benzocaine ointment	—	—	—	—	—	—	—	—	—
Cycloform "	—	—	—	—	—	—	—	—	—
P-aminobenzenesulfamide pdr	—	—	—	—	—	—	—	—	—
Sulfathiazole ointment, pdr	— ¹	++	—	—	—	—	—	++	—
Prontosil pdr	—	—	—	—	—	—	—	—	—
P-aminosalicylic acid pdr, 2 %	—	—	—	++	—	++	++	—	—
P-aminobenzoic acid pdr, "	—	—	—	—	—	++++	—	—	—
P-nitraniline pdr	—	—	—	++	—	++	—	—	—
P-aminoacetanilide "	—	—	—	—	—	—	—	—	—
P-nitrochlorbenzene "	—	—	—	—	—	—	—	—	—
Sodium p-chlorbenzoate "	—	—	+	++	—	—	—	—	—
Amaranth "	—	—	+	+	+	—	—	—	—
Bordeaux BL "	—	—	+++	—	—	—	—	—	—
Neuococcin "	—	—	+++	—	—	—	—	—	—
Orange I "	—	—	+++	—	—	—	+	—	—
Acid yellow "	—	—	+++	+++	+++	—	—	—	—
Patent blue A "	—	—	—	—	—	—	—	—	—
Tartrazine "	—	—	?	+	—	—	—	—	—
Pellidol ointment	—	—	+++	++?	+	—	—	—	—
Methyl orange sat	—	—	?	++	—	—	—	—	—
Nylon stocking as is	—	—	—	++	+	—	—	—	—
Metol 5 %	—	++	+++	+++	++	—	—	—	—
Hydroquinone "	+++	++	+++	++	—	—	—	—	—
Resorcinol 3 %	—	—	?	++	—	—	+	—	—
Catechol pdr	—	—	—	++	—	—	—	—	—
Picric acid 1 %	—	—	+++	—	—	—	—	—	—
Pyrogallol 2 %	—	—	—	—	+	—	—	—	—
Aniline 20 %	—	++	—	++	—	—	—	—	—
Nitrobenzene 20 %	—	—	—	—	—	—	—	—	—
Benzidine udr	—	++	—	+++	—	—	—	—	—
Sodium benzoate "	—	—	—	—	—	—	—	—	—
Sodium salicylate "	—	—	—	—	—	—	—	—	—
Benzyl benzoate 10 %	—	—	—	—	—	—	—	—	—
Naphthylamine pdr	—	++	—	+++	—	—	—	—	—
Beta naphthol "	—	—	—	—	—	—	—	—	—
Anthracene "	—	—	—	—	—	—	—	—	—
Anthraquinone "	—	—	—	—	—	—	—	—	—
Meta-aminophenol "	—	++?	—	—	—	—	—	—	—
Meta-phenylenediamine 2 %	—	++	+++	—	—	—	—	—	—
Meta-toluylenediamine "	+	++?	—	—	—	—	—	—	—
Ortho-aminobenzoic acid pdr	—	—	—	—	—	—	—	—	—
Ortho-toluidin 30 %	—	—	—	—	—	—	—	—	—
Ortho-nitranisol 5 %	—	—	—	—	—	—	—	—	—
Suspected original sensitizer	PPD	?	?	SULF	PPD	?	SULF	PPD	P
Suspected cause of present eruption ...	PPD	?	PROC	PPD	?	?	PPD	?	P

%: aqueous solution

¹: patch test negative, exposition test positive

²: according to history dermatitis occurred after procaine injection

pdr: powder

sat: saturated solution

TABLE I

[illegible]

+?, ++?: not completely certain positive reaction

—?: doubtful reaction (see text)

SULF: sulfonamide

PROC: procaine

NYLON: nylon stocking

TABLE II

Dimethyl-PPD $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{N} \\ \\ \text{C}_6\text{H}_{10} \\ \\ \text{NH}_2 \end{array}$	Metol $\begin{array}{c} \text{H} \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{N} \\ \\ \text{C}_6\text{H}_{10} \\ \\ \text{OH} \end{array}$	P-amidophenol $\begin{array}{c} \text{NH}_2 \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{OH} \end{array}$	Hydroquinone $\begin{array}{c} \text{OH} \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{OH} \end{array}$	Case No
—	±	—	++	1
—	++	—	++	2
—	+++	—	+++	3
++	+++	++	++	4
++	++	++	—	5
—	—	—	—	6
—	—	—	—	7
—	—	—	—	9
—	—	—	—	10
++	—	++	—	11
—	—	—	—	13
++	—	—	—	14
—	—	—	—	20
—	—	±?	—?	23

conclusive are partial investigations. The results discovered with patch tests (see table I) are considered for four similar compounds. Table II shows that metol and hydroquinone and p-amidophenol and dimethyl-paraphenylenediamine seem similar on the basis of skin reactions though one may expect the same as diamethyl-paraphenylenediamine-metol and hydroquinone-p-amidophenol on the basis of chemical structure.

These agents may be found as photo developers and fur dyes in every-day life and the possibility of mutual sensitization could be created in that way. But not much significance is attributed here to this possibility because e.g. there are no photographers, neither are there persons in contact with photographic materials among the patients; they proved to be real "para group" allergic reactors.

The sensitization spectrum was about the same in certain patients in table I, especially in cases 15, 16 and 17 and from

18 to 22 respectively. Similar allergic spectra were found in patients 9, 10 and 12 too. Despite the fact that in cases 9 and 12 we obtained no positive patch reactions except to PPD and acid yellow, we feel justified in including them with subjects sensitized to "para group" because of the positive nylon stocking reaction of subject 10, and of other reactions in the "para grouping", and also because the value of the procaine or sulfonamide *patch test* (16) is not decisive.

We mention case 4, who is interesting because he is similar to *Urbach's* patient (17) who reacted positively to all three dihydroxybenzene derivatives (hydroquinone, resorcinol and pyrocatechol) and it is important not only from a theoretical but from a practical point of view, that four of the patients reacted positively to PAS though they had never taken this drug. We have already emphasized the importance of this finding in connection to PAS (12), recently *Tzanck, Sidi* and *Morrill-Dobkevitch* report 12 similar cases (15) (and a thirteenth case of rubber dermatitis) (16). *Faragó* and *Polgár's* antimycotic, the p-chlorbenzoic sodium (19) showed similar "para group" allergic reactions. With picric acid significance is attributed to the para position of the oxy and nitro groups and to the groups $\text{NO}_2\text{—NH}_2$ (9). In case 5, a positive pyrogallol response cannot be explained on the basis of group allergy, though pyrogallol may be a breakdown intermediate product of some phenolic compounds.

Considering our cases from the point of view of *local anaesthetic allergy* we found that case 6 reacted only to procaine, case 12 on the other hand to all p-aminobenzoic anaesthetics. In cases 20 and 21 local anaesthetic allergy extended also to benzocaine and cycloform which do not contain an amino group in the side chain. We mention here the patient with local anaesthetic allergy, who reacted positively only to anaesthetics containing a tertiary amine in the side chain. It is worth while also to mention here a patient suffering from glaucoma, who was given pontocaine by the ophthalmologist several times. She developed, as could be detected by us, a hypersensitivity only to that local anaesthetic. All this

points to the fact that differences in local anaesthetic allergy may be entirely individual as suggested by *Strauss* (20) and others. Among the latter we mention *Adler*, *Keszyüs* and *Simon* (21), who found a discrepancy between the Landsteiner inhibiting reaction (in experiments with procaine-azoprotein) and the real clinical sensitivity to anaesthetics.

We may confirm also additional observations of previous authors on the basis of our results, e.g. the substitution of the amino group diminishes PPD hypersensitivity (sensitizing power). Diminished reaction can be shown in the same way with dimethyl (ursol DMG), nitro (p-nitraniline), acetyl (p-aminoacetanilide), —OH (p-amidophenol) and then respectively if it is a monoamine (aniline). The reactions to ursol D, which are fewer compared with PPD reactions, agree with *Mayer's* data (3), proving that acetic acid salts of PPD and of similar compounds are weaker sensitizers than the original sensitizers themselves. Also p-aminobenzoic was shown to be a weaker sensitizer than its esters which are used as local anaesthetics.

Neither can we draw further conclusions about azodyes used in colouring food because different results were obtained with amaranth and neucoccin though the chemical difference is only a 3, 7, 4' compared with a 6, 8, 4' salt. We mention however the fact that in the acid yellow, which gives stronger reactions there are 2-2 substituents in the para position (two amines and amino- NaSO_3 respectively) in contrast to Bordeaux BL, which has no para substituents and generally gives negative patch tests on subjects sensitized to "para group". Finally the patent blue A does not belong to the azodye group, only negative patch tests were obtained to this substance in our patients. This indicates that azocolour hypersensitivity usually belongs to "para group" allergy, as stated *Baer*, *Leider* and *Mayer* (5) and as we noticed in case 3 and particularly in case 5.

This latter case seems important enough to be mentioned, because of our success in provoking allergic reactions to food azodyes on a patient sensitized to "para group":

K. K., a woman of 52. She had learnt to sew in 1915 and thus came in contact with textile fabrics, but she discontinued this profession in the same year. In 1935 she developed eruptions on her axillary fold and afterwards on her wrists, elbows and neck due to her first wearing a recently dyed brown blouse, previously blue. From that time till now she frequently had contact eczema on these places, her genital region and face. As she realised, she developed eruptions after wearing black, brown and even blue textile goods. In the winter of 1948 she developed a papular eruption on her fingers due to yellow gloves. Next fall when they had been thoroughly washed the yellow colour faded and she was able to wear them. In the summer of 1949 she reported having a dermatitis on her feet after wearing nylon stockings. She states that she used often to eat candies of different colours, but in the last weeks, so far as she remembered, this did not occur. Other important data including furs, shoes, drugs, cosmetics, etc. are not important in her history, neither could she give any important information concerning her present cutaneous manifestation developed in December 1949.

She was hospitalized on 24th December 1949, with a very itching papular dermatitis on her neck, face, particularly around the eyes, and partially on her ears. A routine examination gave no useful information. Patch tests: see table I, case 5. It should be noted here also that she never used pellidol ointment. It has been suggested that this drug after splitting of the azo-linkage in the skin, is converted to mono- and diaminotoluene which differ only in a methyl group from aniline, and PPD. Mayer stated in his ursol experiments that allergy to pellidol indicates a high degree of quinone sensitization (22).

Two days after she had been treated with various ointments and antihistaminics she was greatly improved. The role of the azodyes was further investigated at certain intervals.

XII. 27: 200 mg. *acid yellow* mixed with jam was eaten: during the night she had a localized irritation of the back (site of patch reaction? see also case 1 below) and on the next day she developed a new papular eruption on her neck and face. A control had no complaints. Exposition test: *positive*.

XII. 30: 200 mg. *acid yellow* + sugar + quince jelly ingested: no complaints. Exposition test: negative.

1950. 1.2: she was given 200 mg. *acid yellow* + alcohol (60°) + sugar: in the evening irritation and appearance of *new* lesions on neck, however not as accentuated as on December 28th. Control subject: no evident irritation or dermatitis. Exposition test: *positive*.

1.7: ingestion of 200 mg. *amaranth* mixed to jam: next morning pruritus and *new* papular dermatitis on neck. Control had no complaints. Exposition test: *positive*.

Eating 15 mg. of candy: no change.

We also performed an ingestion test with *phenacetine* chemically related to p-amidophenol, however this drug produced no reaction.

The acid yellow which twice gave positive results on ingestion is a mixture of mono- and disulfonic sodium of 4-amino-azobenzene. On the basis of its chemical structure one may expect splitting and conversion to a quinone compound. It is closely related to yellow 6 (1-p-sulfophenylazo-naphthol-6-sulfonic disodium), and *Baer* and *Leider* (23) saw pruritus in their PPD sensitive patients due to this compound. Not possessing this compound we did an ingestion test with amaranth (see table I) stated to cause a positive patch reaction and having two azo-linked naphthalene rings. This azodye also gave a positive reaction with an exposition test. With amaranth one wonders whether naphthalene compounds are able to sensitize or elicit allergic reactions either by quinone or by other group mechanisms. As we know, naphthols and naphthalene could be transformed into a quinone compound (naphthoquinone) by chemic processes, it can be supposed that the same happens in vivo.

The azodye mixtures used in our ingestion experiments proved to be free from disagreeable intestinal effects in control subjects too. The latter were patients suffering from contact eczema and giving negative patch results to PPD, nylon, acid yellow and amaranth.

Finally while we could not detect the cause of the last eruption developed in December 1949 of case 5, it could be concluded, that besides positive patch test reactions to PPD, nylon stockings and other similar compounds, the patient could not tolerate azodyes used to colour foods in our country. Among the latter we could obtain with acid yellow and amaranth positive patch reactions as well as positive ingestion tests. The ingestion of 200 mg. of acid yellow and of amaranth caused *new* papular eruptions proving immunological connections between azodyes colouring food and "para group" compounds (5), and eliciting by internal way allergic reactions on the subject probably sensitized by external contact with PPD.

It is a well known phenomenon in *drug allergy* that only an exposition test is decisive in cases of sulfonamide or pro-

caine hypersensitivity, while skin tests may be negative. We reported also similar cases in table I (cases 1, 3, 21 and 22). It also may be noted regarding case 1, that he felt severe irritation of the back after drinking, as a test, a "cherry" drink containing azocolours. It could not be established, however, conclusively whether this local reaction corresponded to the site of a former PPD patch.

We endeavoured to elucidate the *original sensitizer and the eliciting "para compound" too* (see table I). Cases 1 (man, aged 35, textile dyer), 8 (man of 37, technician, former textile technician), 11, 12 and 13 (hairdressers) are of *professional* origin. Case 11 had to discontinue her profession of hairdresser 15 years ago, because she was suffering from hand eczema. She had her hair dyed and developed an eruption two days later as a result. Case 14 (a man of 29, employee) bought a hairdye and smeared his hair with it. After 5 days he developed a dermatitis on his scalp and forehead and had fever. In this case the original sensitizer and provoking agent are the same and we observed the development of the sensitization. The original sensitizers and eliciting "para group" compounds are the same in other cases too, mainly in our cases of procaine sensitivity, besides the previously mentioned hairdressers, textile dyer and cases 9, 15. The latter used hairdyes for years, thus PPD (p-amidophenol or other similar substances?) was the common original sensitizing "para group" agent.

In cases 19, 20 and 21, inflammation developed due to ointments containing *procaine* (chiefly haemorrhoidal ointments) or to procaine injections. We emphasize here too the not infrequent sensitizing role of procaine, which may be considered as a "specific" therapeutic agent of perianal pruritus and dermatoses.

It may be of interest to mention case No. 12, who is a hairdresser who has done hairdyeing for five years. She developed hairdye dermatitis following ingestion of sulfonamide a year ago. This fact may be explained by the sensitizing effect of sulfonamides to "para group" compounds. It

may be noted that she showed an allergic patch test reaction to cold wave lotions too, and it is of special interest that she has a history of tolerating procaine when 8 of her teeth were extracted 2-3 years ago. Case 18 is exactly the opposite: a barber, aged 43, developed a dermatitis due to ointments containing procaine used against haemorrhoids. Here the dye (PPD) used in his profession was the original sensitizer, while the drug (procaine) the sensitivity eliciting "para group" compound. *Tzanck* and his school describe similar cases (24, 25, 16).

In case 10 the reason that she developed an eruption on her feet after first wearing dark nylon stockings may be explained by sensitization to *sulfonamides* extending to "para group" compounds.

Sulfonamides were used for many years in the treatment of meningitis and chronic cystitis. This case—similar to case 5—completely agrees with *Baer* and *Leider's* findings (23), attributing only a secondary role to azodyes in sensitization. This means that azodyes are capable of eliciting skin reactions in "para group" allergic subjects but are weak sensitizers.

Case 7 is of interest too in that he tolerated sulfonamide extremely well whether given as an ointment or as tablets and also an injection of procaine, yet he was sensitized to "para group". While in contrast to this case and case 12, we are justified in introducing contraindications with compounds and drugs of the "para group" for subjects sensitized to "para group", corresponding to the reports that sensitization develops more easily in these people. This has also been proved recently by *Sidi* and *Dobkevitch-Morrill* (16) by ingestion and injection of "para group" substances on subjects sensitized to "para group", usually eliciting positive local and general reactions. In case 7, the sulfonamide skin reactions were negative, which is not surprising when the above facts are taken into consideration. It should be noted however that positive reactions were obtained less frequently either on intact or glasswool abraded skin, than by *Tzanck* and his collaborators in cases of sulfonamide hypersensitivity.

From the practical point of view, we could give in most cases of procaine sensitivity *percaine* (nupercaine) as a local anaesthetic without danger. In his investigation of itching anal complexes, *Böhm* (26) reports to have made patch tests with the agents concerned. He found among 700 such patients, 19 reacted to procaine and 10 to percaine (0.1 %). In cases of procaine sensitivity alypin (benzoic acid methyl-diaminopentanol) was given. The high incidence of percaine hypersensitivity found is due in our opinion to the fact that contrary to our practice percaine (nupercaine) is a frequently used local anaesthetic in Switzerland.

We cite one of our procaine dermatitis cases as a characteristic example of a developing sensitization. It shows the *sensitization promoting effect of trauma (burning)*:

F. L., a female of 37, employee in a pharmaceutical factory (not identical with patient 7 in table I). In 1936 a glass vessel containing boiling procaine broke in her hands and the hot fluid poured over both her hands and forearm. Since that time vesicles develop on her hands whenever she is in contact with procaine. Dermatitis developed on the previously burned sites some hours after a dentist's procaine injection. In 1946 again after a procaine injection for a tooth extraction during surgical treatment of a boil on her right arm, a strong flare up developed again on the sites after application of a local anaesthetic. When we examined her, the dermatitis had disappeared. Now the patient wants to have a tooth extracted, but she is afraid of procaine and sought our advice. Procaine 1/2 % intracutaneously, immediate reaction: negative, delayed: positive. Patch tests: procaine: ++, pontocaine: ++, percaine: negative. Patch tests also provoked focal reactions: old sites itched and became slightly inflamed.

The role of burning may be seen in case 15 too. The hairdresser burned the patient's skin by her second application of hair-dye. After three days she developed a pyoderma starting and extending from the burned site and after 6 days she had a general rash. Burning was here promoting not only chemical but also coccogenic sensitization and a role should be attributed to both factors. In case 7 the patient stated that she had a dermatitis on the dorsa of her feet following an irritation from a shoelace. She wore slippers at home, which were trimmed with black fur. This was in permanent contact with

her inflamed skin. She felt it irritating, and on her daughter's advice she removed the fur trimming. After this, her skin calmed down.

Coming to another pathological problem, there is some difficulty in connection with *aniline*, for it gives cross reactions with substances of the "para group" being a monoamine, though not a "para group" compound. Some try to overcome this difficulty with the suggestion that some substituent or compound of para structure gets into the aniline molecule in vivo. It seems to us however simpler and more acceptance an explanation, that by the transformation of aniline to quinone in the organism—as *Mayer* (3, 4) established—the breakdown derivate *p-amidophenol* is the link. This having a para structure helps us to understand the aniline-"para group" compound cross reaction. It is however necessary to mention that according to our results the aniline and *p-amidophenol* skin reactions do not run parallel (see table I). Nevertheless the intermolecular breakdown and rearrangement allow a reasonable explanation to be made for cross relationship between substances apparently unrelated.

Following the ideas in *Tzanck's* recent book (25) we performed patch tests also with *rubber components* in some cases. We believe rubber accelerators belonging to the "para group" compounds are of importance here. However we have no positive reaction with these substances. The same applies to neoarsphenamine which has two hydroxy and -As-groups in the para position (see table III). According to their history, rubber boots and gloves (e.g. case 7) were well tolerated by our patients. In case 13 it can be noted that he worked in a shoe factory with brown and dark coloured leather (PPD!) He was, however, dealing also for a short time with crêpe and other sorts of rubber.

Finally we emphasize again the important *practical consequences* of the problem. All patients who react with allergic symptoms to any of the sulfonamides, PAS, *p-aminobenzoic acid*, procaine (pontocaine, benzocaine) and other drugs of para (para-amino-) structure are to be treated with great care

TABLE III

Cases:	7.	8.	12.	13.	15.
Aldole-alpha-naphthylamine rubber accelerator	—		—	—	—
Dibenzothiazyl disulfide rubber accelerator ...	—		—	—	—
Mercaptobenzthiazole rubber accelerator	—	—			
Ureka rubber accelerator	—	—			
Rubber, crêpe				—	
Rubber, hycar	—			—	
Rubber, smoked	—				
Rubber, dye, blue				—	
Cresol 2 %			—	—	—
Neoarsphenamine 10 %			—	—	—
Neoarsphenamine 10 % with scarification			—	—	++?
Neoarsphenamine 10 % abraded with glass ...			—	—	—
Streptomycin				—	

and only after negative skin tests should these substances be carefully given. Drugs having the same effect, but of another chemical structure (e.g. penicillin, D₂-vitamine, nupercaine and so on) should be tried in these cases. Patients suffering from hair-, cloth-, food dye hypersensitivity may also belong to subjects sensitized to "para group" and are affected by drugs of para structure, especially the strong sensitizing sulfonamides, procaine (pontocaine, benzocaine), PAS may create a relative contraindication for them too. At our department we give a certificate to the patient sensitized to "para group" on his allergic state and list the allergens he has to avoid and thus we assume he is able to prevent allergic symptoms of these drugs by showing this certificate to any physician or chemist.

SUMMARY

1. Hypersensitivity to the "para group" on the basis of positional isomery is a good example of the connection between chemical structure and sensitization. This is pointed out by several authors.
2. We performed patch tests on 23 subjects with several substances. The results collected in table I demonstrate that they belong to subjects sensitized to "para group".

However it could not be predicated in the *individual case* which compound of the "para group" are included in the allergic spectrum of the patient. The supposed cause of individual differences on subjects sensitized to "para group" is that we do not know the way and mechanism of the transformations of chemical allergens in the organism. It seems that a chemical allergen is apt to produce sensitization and elicit allergic reactions linked as a hapten to proteins (conjugated allergen) in certain cases, while in others differently linked from a qualitative and quantitative point of view, this does not occur.

3. The difficulties in connection with chemical structure and sensitization are shown on similar patch test results between metol and hydroquinone and between p-amidophenol and dimethylparaphenylenediamine in contrast to the expected data on the basis of chemical structure.
4. A case of a woman is reported, who proved to be sensitized to paraphenylenediamine, nylon dye and other substances of the "para group". The ingestion of 200 mg. of *acid yellow* was repeatedly followed by the appearance of *new* papular lesions. Administration of 200 mg. of *amaranth* had the same effect on the patient. Acid yellow and amaranth are azodyes used to colour foods in our country.
5. We endeavoured to elucidate in all our patients *the original sensitizer and the eliciting "para group" substance*. The role of *profession* (e.g. hairdresser, textile dyer) and of the importance of frequent procaine administrations (perianal pruritus and dermatoses) is emphasized.
6. The results of investigations of "para group" hypersensitivity adds further data to the study of cross reactions and the mechanism of internal-external sensitization. We cite some of our interesting cases related to this point.
7. At our department we give a certificate to the patient sensitized to "para group" on his allergic state and list the allergens he has to avoid and thus we assume he is able to prevent allergic symptoms from them by showing this certificate to any physician or chemist.

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