Occupational Dermatoses from Colour Developing Agents

Clinical and Histopathological Observations

CAROLA LIDÉN[1, 2] and EVA BREHMER-ANDERSSON[3]

[1]*Division of Occupational Dermatology, National Institute of Occupational Health, Solna,*
[2]*Department of Occupational Dermatology, Karolinska Hospital, Stockholm, and*
[3]*Department of Pathology, Södersjukhuset, Stockholm, Sweden*

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Exposure to colour developing agents that are derivatives of p-phenylenediamine, e.g. CD-2 and CD-3, are known to cause lichenoid lesions and allergic contact dermatitis. This study describes the clinical picture, course and patch test results in 24 patients with occupational skin disease caused by colour developing agents. Biopsies for histopathology of the occupationally-induced lesions and/or patch test reactions were obtained in 14 cases. The skin lesions cleared rapidly after exposure to colour developers had ceased. Sixteen patients had to leave their exposed work due to the skin disease. Contact allergy to colour developing agents was found in 23 cases. The clinical and histopathological findings showed that lichen planus and lichen planus-like lesions were common among the dermatoses caused by colour developers. It was not possible to provoke lichenoid lesions by patch testing. The histopathology of the patch test reactions showed dermatitis. *Key words: Contact allergy; Lichenoid reaction; Patch testing.* (Received May 13, 1988.)

C. Lidén, Division of Occupational Dermatology, National Institute of Occupational Health, S-171 84 Solna, Sweden.

Chemicals used for processing photographs have been known since the beginning of the century to be hazardous to the skin and to cause occupational dermatoses among photographers (1). Many of these chemicals are described as irritants or allergens (2–5). Particular attention has been paid to the colour developing agents which are derivatives of p-phenylenediamine. In 1958 Buckley (6) and Graciansky et al. (7) were the first to report that colour developers could give rise to lichen planus and lichen planus-like eruptions, besides the previously reported allergic contact dermatitis (8). Several reports on lichenoid reactions from colour developing agents have since been published, mainly case reports but also a few field studies (for references, see (5)). Most of the cases of lichenoid skin lesions showed a positive patch test reaction to the colour developer in question (6, 7, 9–11). In a few patients, histopathological investigations have been performed on lichenoid skin lesions and patch test reactions (6, 7, 11–15).

In studies concerning skin reactions due to colour developing agents, the following aspects have been discussed: whether the lichenoid reaction from colour developers is genuine lichen planus or a variant of allergic contact dermatitis; the relation between dermatitis and lichenoid reaction; whether the exposure triggering the lichenoid reaction is topical or systemic; and also the question of cross-reactivity between different colour developers (6–12, 15–17).

The present study describes the clinical picture and course of skin lesions caused by colour developing agents in 24 cases. In 14 of these, histopathology of the occupationally-induced skin lesions and/or patch test reactions was also investigated.

MATERIALS AND METHODS

Patients

The study is based on 24 cases that according to history, clinical picture and patch test results were considered to have dermatoses caused by colour developing agents. Seventeen cases (cases 1–10 and cases

11–17) were included from two field studies concerning occupational dermatoses at two large movie film laboratories, carried out during 1979–86 (5, 18). Seven cases (cases 18–24) were patients referred to our Department, during the same period, from these and other film laboratories. All but one (case 12) were men. Cases 18 and 19 were brothers.

Clinical examination and interview

The skin lesions were examined by one of the authors (C. L.) in 14 cases, and by other dermatologists in 5 cases. In 5 other cases, obtained from the field studies, the rash had cleared before the examination. Seen with the naked eye, the lesions were classified as dermatitis (used synonymously with eczema), lichen planus, or a combination of dermatitis and lichen planus. The latter two groups will be referred to as lichenoid reactions. Lesions consisting of erythema, papules, vesicles, scaling, crusting and excoriations in combination were diagnosed as dermatitis. Flat, polygonal, violaceous, shiny papules, in some cases with residual pigmentation, were classified as lichen planus. Cases in which lesions typical for both dermatitis and lichen planus were simultaneously present were classified as being of the combined type.

Interviews concerning exposure to colour developers and history of the skin disease were carried out by one of us (C. L.). In a few cases the rash had first appeared several years previously.

Patch testing

CD-2 and CD-3 are the colour developers used at movie film laboratories, and CD-3 and CD-4 are used for amateur film. CD-1 and CD-6 are rarely used in Sweden. All cases were patch tested with CD-2 and CD-3, 1% in petrolatum or water (2–4), case 17 also with CD-1, and case 23 with CD-1, CD-4 and CD-6. Serial dilution tests with CD-2 (0.1, 0.01, and 0.001%) were done in cases 1 and 14. All cases were tested with the main part of the standard tray at our Department, and with Metol and hydroquinone 1% in petrolatum. Additional tests were applied when indicated by the history. The standard test substances were supplied by Trolab (Hellerup, Denmark), Hermal-Chemie (Reinbek-Hamburg, FRG) and Epitest Oy (Helsinki, Finland). CD-2, CD-3, Metol and hydroquinone were from Kodak or Merck, of commercial quality and of unknown purity. Finn-Chambers® (Epitest Oy), Al-test® (Imeco, Södertälje, Sweden), and Scanpor® surgical tape (Norgesplaster, Kristiansand, Norway) were used.

The patches were removed after 48 h and readings were made 72 h after application. In 18 cases a second reading was made after 2–3 weeks. Minimal criteria for a positive reaction at the 72 h reading were erythema and infiltration. At the 2–3 week reading, erythema, scaling or shiny small papules were also judged as positive reactions. Between the first and the following readings the test sites were marked with a special pen.

Skin biopsies

Punch biopsies for histopathological examination were obtained from 14 cases. In 9 cases, biopsies were taken both from occupationally-induced skin lesions and from positive patch test reactions, in 2 cases from occupationally-induced lesions only, and in 3 from patch test reactions only. In all cases, biopsies from test reactions were taken at 48–72 h after application of the patches. To find out the best moment for taking the biopsies, specimens were also obtained, in 8 cases, at different intervals 1–5 weeks after application. The optimal time was found to be at 48–72 h. Later on, the histopathological findings diminished. By applying the appropriate number of patches it was possible to take only one biopsy from each patch test site. The test substance was in all cases CD-2. Biopsies were taken also from two CD-3 test reactions and one CD-1 reaction. Ethylchloride spray anaesthesia and 3 mm or 4 mm punches were used. The specimens were fixed in 10% formalin, embedded in paraffin and processed. All were stained with hematoxylin-eosin and most also with PAS and by the van Gieson method.

RESULTS

Exposure and course of skin disease

The mean age of the workers at the *onset* of the occupational dermatoses, suspectedly caused by colour developing agents, was 28 years (range 18–50). At the onset 11 worked as chemical mixers, 9 as developers, 2 as maintenance technicians and 2 as analysists (Table I). The time in chemically exposed work, when they fell ill, was less than one year for 12 cases. Nine of the 11 chemical mixers got their skin disease within one year, and 6 of them within 6 months after introduction to the job. Sixteen of the patients had to leave their chemically exposed work due to skin symptoms, 2 changed job due to other reasons, and 6 continued

to work in chemical exposure. Three developers continued for more than 10 years after onset (case 11, 32 years; case 4, 27 years; case 3, 11 years, respectively). Patients 11 and 4 still manage thanks to meticulous hygiene. Patient 3 was forced to leave this work because of the skin disease. 18 years later he could not even pass the developing hall without getting a rash on his hands and face.

Clinical picture

The 19 patients examined by dermatologists were given the diagnoses dermatitis (7 cases), lichen planus (5 cases) and combined (7 cases) (Table II). Table I shows the clinical picture, distribution observed and stated maximum distribution in the individual cases. The 5 cases with clinical lesions classified as lichen planus were macromorphologically indistinguishable from genuine lichen planus. The 7 cases classified as a combination of dermatitis and lichen planus presented—besides the typical lichenoid eruptions—moderate scaling, but also lesions on the face. In the 2 cases with penile lesions, these were localized to the shaft only. Oral lesions were not found.

The course of the rash—dermatitis, lichen planus, and the combined type—was in all cases closely related to exposure to colour developers. The lesions cleared within a few weeks after the exposure had ceased and they recurred on re-exposure.

Table I. *Task at onset of occupational dermatoses. Clinical diagnoses, distribution observed and stated maximum distribution caused by colour developing agents*

		Clinical diagnoses			Distribution observed			Maximum distribution stated		
Case no.	Task[a]	Dermatitis	Lichen planus	Comb	Hands/ forearms	Face	Other[b]	Hands/ forearms	Face	Other[b]
1	Dev	–	–	+	+	–	–	+	–	+ (f)
2	Ana	+	–	–	+	–	–	+	+	+ (a, f, t)
3	Dev	+	–	–	+	+	–	+	+	–
4	Dev	–	–	–	–	–	–	+	+	+ (l)
5	Mix	+	–	–	+	+	+ (l, t)	+	+	+ (t)
6	Mix	+	–	–	+	–	–	+	–	–
7	Mix	–	–	+	+	+	+ (f, p, t)	+	+	+ (f, p, t)
8	Dev	–	+	–	+	–	+ (a)	+	–	+ (a, g, l)
9	Dev	+	–	–	+	+	+ (n, t)	+	+	+ (n, t)
10	Work	–	+	–	+	–	–	+	–	+ (a, f)
11	Dev	+	–	–	+	–	–	+	–	–
12	Ana	–	–	–	–	–	–	–	+	–
13	Mix	–	–	–	–	–	–	+	–	–
14	Mix	–	+	–	+	–	–	+	–	–
15	Work	–	–	–	–	–	–	+	–	–
16	Mix	+	–	–	+	–	–	+	–	–
17	Dev	–	–	–	–	–	–	+	–	–
18	Mix	–	+	–	+	–	–	+	–	–
19	Mix	–	+	–	+	–	–	+	–	–
20	Mix	–	–	+	+	+	+ (f, p)	+	+	+ (f, p)
21	Dev	–	–	+	+	–	+ (a, p, t)	+	–	+ (a, p, t)
22	Dev	–	–	+	+	–	–	+	–	–
23	Mix	–	–	+	+	–	+ (a)	+	–	+ (a)
24	Mix	–	–	+	+	+	+ (n)	+	+	+ (n)
		7	5	7	19	6	8	23	9	12

[a] Mix = mixing; Dev = developing; Work = workshop; Ana = analysis.
[b] a = axillae; f = feet; g = groins; l = legs; n = neck; p = penis or scrotum; t = trunk.

Patch testing

Table II shows the patch test results related to the diagnoses. At the 72 h reading, 22 of the 24 cases proved positive to CD-2 and 8 to CD-3. The number of positive patch test reactions to other substances were: CD-1, 2; CD-4, 1; CD-6, 1; Metol, 4; PBA-1, 3; hydroquinone, 1 and p-phenylenediamine, 2.

Two cases (cases 10 and 17) proved negative to both CD-2 and CD-3. Patient 10, a maintenance technician, had for many years experienced a rash in connection with cleaning CD-2

Table II. *Clinical diagnoses in 19 cases of skin disease due to colour developing agents. The remaining five cases had cleared at the examination. The patch test reactions to CD-2 or CD-3 at 72 h and 2–3 weeks are given*

Pos 2–3 w = Erythema, scaling, and shiny small papules also included, see text. N.e. = Not examined by the author

Clinical diagnosis	No. of cases	Patch test reactions at 72 h Pos	72 h Neg	2–3 w Pos	2–3 w Neg	2–3 w N.e.
Dermatitis	7	7	0	3	1	3
Lichen planus	5	4	1	1	3	1
Combined	7	7	0	6	0	1
Cleared rash not examined	5	4	1	2	2	1
Total	24	22	2	12	6	6

Table III. *Clinical diagnoses and histopathological findings in occupationally-induced skin lesions and patch test reactions at 48–72 h from colour developing agents*

n.e. = not examined; n.o. = biopsy not obtained

Case no.	Occupationally induced skin lesion: Clinical diagnosis	Occupationally induced skin lesion: Histological picture	CD-2 patch test site: Test reaction	CD-2 patch test site: Histological picture
1	Combined	n.o.	Pos	Dermatitis
3	Dermatitis	n.o.	Pos	Dermatitis[a]
4	n.e.	n.o.	(Pos)[b]	Normal
7	Combined	Combined	Pos	n.o.
8	Lichen planus	Lichen planus	(Pos)[b]	Unspecific
10	Lichen planus	Combined	Neg	n.o.
14	Lichen planus	Dermatitis	Pos	Dermatitis
18	Lichen planus	Combined[c]	Pos	Dermatitis
19	Lichen planus	Combined	Pos	Unspecific
20	Combined	Combined	Pos	Dermatitis
21	Combined	Lichen planus	Pos	Dermatitis
22	Combined	Dermatitis	Pos	Dermatitis[d]
23	Combined	Dermatitis	Pos	Dermatitis[d]
24	Combined	Dermatitis	Pos	Dermatitis[d]

[a] Biopsy at 1 week due to technical failure at 72 h.
[b] Biopsy from weak reaction graded (pos), but judged as positive at previous test.
[c] Predominantly lichenoid.
[d] Biopsy from a positive CD-1 or CD-3 test reaction, as well, showed dermatitis at histopathology.

tanks. He showed a lichen planus-like rash on the forearms after heavy exposure to CD-2. It disappeared within 2 weeks when he was absent from work and recurred on re-exposure. Patient 17 was separately tested with CD-1 and found positive, which was in accordance with the history. Patient 22 was positive to CD-2 and CD-3, yet he had only worked with CD-3. Patient 23 was patch tested with the developers CD-1, CD-2, CD-3, CD-4 and CD-6. He proved positive to all but CD-3. However, he had experienced exposure only to CD-3 and CD-4 at work.

At the second reading—after 2–3 weeks—12 of 18 cases were still positive to CD-2, and 6 to CD-3. Seven of them (cases 1, 3, 4, 12, 21, and 23) showed red or shiny small papules at the test site, and five (cases 2, 9, 20, 22, and 24) showed erythema and/or scaling. Thus, positive reactions at 2–3 weeks, as well as negative test sites, were found among patients both with dermatitis, lichen planus and the combination (Table II). No reaction negative at 72 h had turned positive at 2–3 weeks.

Histopathological findings (Table III)

In 11 cases skin biopsies were taken from occupationally-induced skin lesions. In 2 cases (cases 8 and 21) the histopathological picture was indistinguishable from that of lichen planus. In 4 cases (cases 14, 22–24) the picture was that of dermatitis with slight acanthosis, spongiosis, slight exocytosis and small perivascular infiltrates of lymphocytes in the upper dermis. In one of these cases with rather marked spongiosis there was also a subepidermal vesicle, and in some cases there were several apoptotic bodies (previously called colloid or Civatte's bodies) in the epidermis. In 5 cases (cases 7, 10, 18–20) the lesions exhibited a mixture of chronic dermatitis and lichen planus, i.e. there was a moderate dermatitis with small lichen planus-like areas (Fig. 1 *a*). In 3 cases there were in addition conspicuous accumulations of apoptotic bodies mixed with lymphocytes at the epidermal–dermal junction (Fig. 1 *c*). The apoptotic bodies were in most cases PAS-negative, in some cases slightly PAS-positive, and stained slightly yellow according to van Gieson.

In 12 cases, biopsies were taken from patch test reactions caused by CD-2. The histopathological descriptions refer to biopsies taken 48–72 h after application, except in case 3 where the one-week biopsy had to be used because of technical failure. In 8 cases (cases 1, 3, 18, 20–24) the biopsies disclosed dermatitis with spongiosis and exocytosis and in some of them also small vesicles (Fig. 1 *b*), intra-epidermal apoptotic bodies and subepidermal oedema. In one case (case 14) the test reaction exhibited acute dermatitis with many eosinophils and marked subepidermal oedema. One biopsy from a CD-3 reaction and one from a CD-1 reaction showed dermatitis. One biopsy (case 4) showed normal skin and two (cases 8 and 19) only very discrete perivascular lymphocyte infiltrates.

DISCUSSION

The previous reports on skin lesions due to colour developers, mostly case reports, do not indicate the frequency of lichen planus and lichenoid reactions versus dermatitis. In the present study the skin lesions were examined clinically in 19/24 cases. Cases of lichen planus-like lesions or a combination of lichenoid lesions and dermatitis together made up the main part, 12 cases (Table II). From 11 of these 19 cases biopsies from occupationally-induced skin lesions were obtained, and the histopathological picture was that of dermatitis, lichen planus or a combination of lichen planus and dermatitis (combined lesions) (Table III). It was easy to tell dermatitis from lichen planus or lichenoid lesions, but sometimes difficult to judge a lesion as lichen planus or combined. Therefore these two kinds of lesion make up a histopathological group (7 cases). Four cases clinically judged as combined and one as lichen

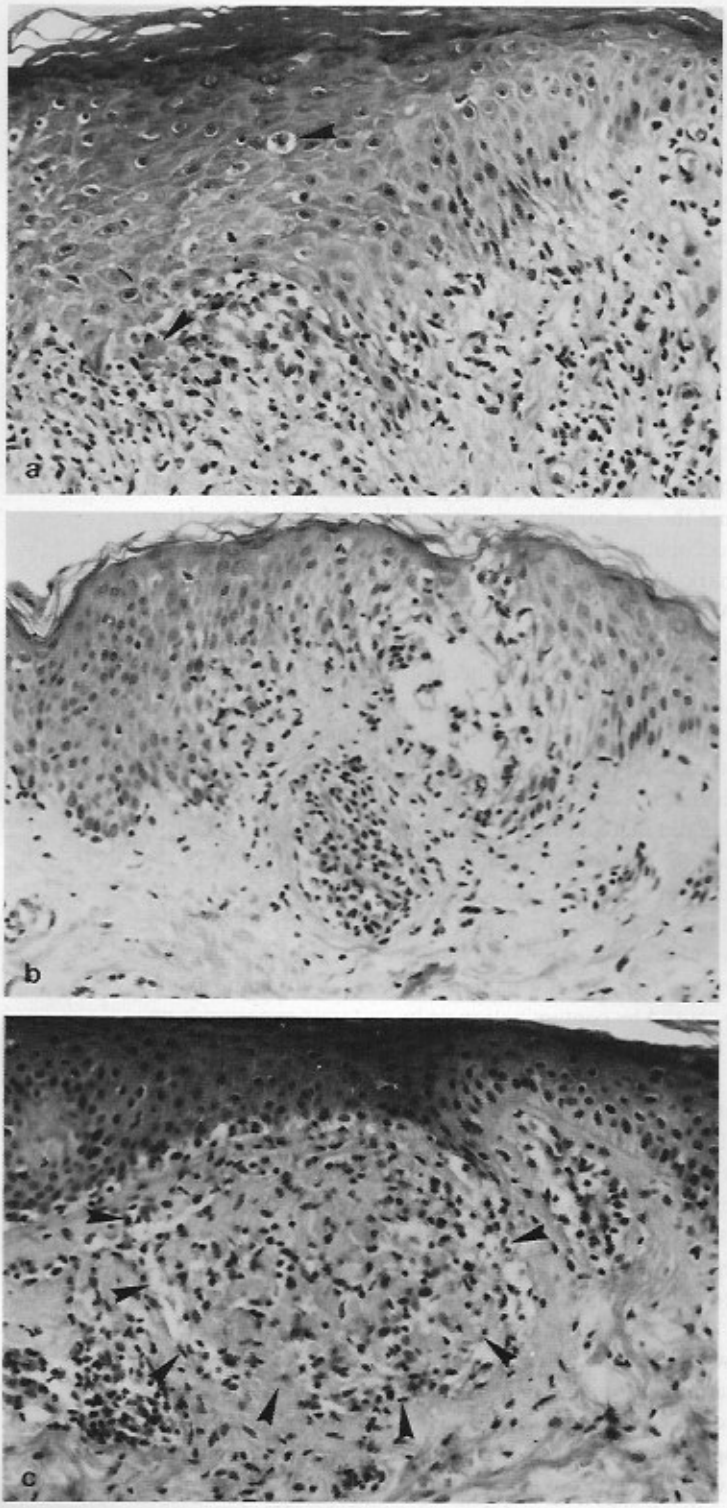

Fig. 1. (*a*) Biopsy from an occupationally-induced skin lesion in case 18, showing a lichenoid picture with typical 'saw-tooth' rete ridges and a subepidermal infiltrate of lymphocytes. There is an apoptotic body in the middle of the epidermis and one at the epidermal–dermal junction (*arrows*). (*b*) Biopsy from a positive test reaction to CD-2 in the same case displaying vesicular dermatitis. (*c*) Biopsy from an occupationally-induced skin lesion in case 19. A host of apoptotic bodies connected to lymphocytes is situated below the epidermis.

planus were histopathologically classified as dermatitis. All biopsies taken from positive test reactions, except 3 with normal or near-normal histology, showed the picture of dermatitis.

Considered together, the clinical and histopathological findings denote that lichen planus and lichen planus-like lesions are rather common types of skin lesion in dermatoses caused by colour developers. Further, there is no clear-cut boundary between lichen planus and combined lesions, and dermatitis. This mixed clinical and histopathological picture and the positive test reactions speak against the hypothesis that lichen-like lesions due to colour developing agents represent a genuine lichen planus. The observation that the skin lesions cleared a few weeks after exposure to the colour developing agents had ceased also supports this interpretation. A rapid disappearance of the rash when exposure to developers stopped was also noted by Buckley (6), Fry (11) and Mandel (10). Genuine lichen planus often has a more protracted course (19, 20). In a study of 79 cases of genuine lichen planus it was further shown that these patients were patch test negative to CD-2 and CD-3 (20).

In the literature we have found histopathological descriptions of lichenoid skin lesions in 14 cases and of test reactions in 3 (7, 11–15), and they agree with our findings. Thus in the studies mentioned, the lichenoid skin lesions showed the picture of either lichen planus or of both lichen planus and dermatitis, and the test reactions examined showed dermatitis. However, in 3 of our cases the biopsy of occupationally-provoked lesions revealed, in addition to these more ordinary reactions, remarkable accumulations of apoptotic bodies at the epidermal–dermal junction (Fig. 1 *c*). Also in some biopsies disclosing dermatitis, both from occupationally-induced lesions and test sites, there were numerous apoptotic bodies in the epidermis. Apoptosis is a kind of cell death different from necrosis, and it is a physiological phenomenon. It is however also induced in target cells by attachment of specifically stimulated T-lymphocytes, and is exacerbated by conditions in which cell-mediated immune reactions are involved, such as lichen planus and drug eruptions are thought to be. Weedon et al. (21) noted extensive apoptosis in histological sections of fixed drug eruptions.

It has been suggested that the lichenoid reaction from colour developing agents is caused by systemic exposure, e.g. by inhalation, ingestion or skin absorption, because some of the patients had lichenoid lesions on the trunk, penis, scrotum, thighs or axillae (6, 7, 9–12, 15, 16). Oral lesions have been reported only in 2 cases, by Graciansky et al. (7, 16). Most of the patients in our study (Table I) showed lichenoid lesions only in areas in direct contact with the colour developer. No oral lesions were found. A few patients showed lesions in the axillae and the groins. Whether these were caused by contamination or by systemic exposure is unclear. The general impression was, however, that direct contact was the main cause of the lichenoid reactions.

Cross-reactivity between different colour developers and p-phenylenediamine, and their different sensitizing properties, has been discussed (5, 6, 10, 11, 17, 22). The results from the present study indicate the possibility of cross sensitivity (patients 22 and 23 were positive also to colour developing agents that they had not been exposed to). However, this question has been studied in animal experiments in combination with chemical analysis of the test preparations, and the results will be reported separately (23, 24).

The colour developers were tested at 1% in petrolatum, and in some cases also at 1% in water, and at lower concentrations. The concentrations were those recommended in the literature (2–4). Tests in 200 controls with 1% of CD-2 and CD-3, and in 450 controls with 1% of CD-1, CD-4, and CD-6 in petrolatum have been done. This concentration is adequate in the sense that it does not give rise to false-positive reactions (5, 18). However, it is possible that the concentration is too low, especially for CD-3 with its higher molecular weight. This might be the explanation for some cases with a convincing history, but with negative patch tests. Patch testing with p-phenylenediamine has caused flare-up reactions (25), but in our study none was observed either from p-phenylenediamine or from the colour developing

agents. Another photographic chemical, PBA-1, gave rise to flare-up reactions (5, 26). This might speak against a rise of patch test concentrations for colour developing agents.

In this study, 16/24 persons had to change job because of dermatoses caused by colour developing agents. Other allergens and irritants must however not be forgotten when examining patients from this work environment (3–5, 26). Four of our patients (cases 2–4, 11) got their first symptoms during the 1950s, and since then the film laboratories have been modernized. But the chemical exposure is still heavy, especially for the chemical mixers.

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