Review Article

Medical & Clinical Research

Cosmetic Allergen in the Past and Present

Hideo Nakayama[1], Tamotsu Ebihara[2] and Ko-Ron Chen[1]

[1]*Meguro Chen Dermatology Clinic, Tokyo, Japan.*

[2]*Departments of Dermatology, Keio University Hospital, Tokyo, Japan.*

***Corresponding author**
Hideo Nakayama M.D, Departments of Dermatology, Meguro Chen Dermatology Clinic, Tokyo, Japan.

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Abstract

For almost 20 years after the end of World War II, many Japanese women were challenged by a dark secondary hyper pigmentation on their faces. The causation of this condition was unknown and incurable at the time. However this symptom became curable after a number of new cosmetic allergens were discovered through patch tests and as an aftermath, various cosmetics and soaps that eliminated all these allergens were put into production to be used exclusively for these patients.

An international research project conducted by seven countries was set out to find out the new allergens and discover non-allergic cosmetic materials. Due to these efforts, two disastrous cosmetic primary sensitizers were banned and this helped to decrease allergic cosmetic dermatitis. Towards the end of the 20th century, the rate of positives among cosmetic sensitizers decreased to levels of 5% - 8% and have since maintained its rates into the 21th century.

Currently, metal ions such as the likes of nickel have been identified as being the most common allergens found in cosmetics and cosmetic instruments. They often produce rosacea-like facial dermatitis and therefore allergen controlled soaps and cosmetics have been proved to be useful in recovering normal skin conditions.

Keywords: Cosmetic Dermatitis, Cosmetic Allergy, Metal Allergy, Patch Test, Allergen Control.

Introduction

Cosmetics and toiletries are made by human beings and hence are innumerable number of companies that produce them. Medical history shows that there have been a number of cosmetic ingredients which produced allergic cosmetic dermatitis and irritant cosmetic dermatitis. For almost 20 years after World War II, many Japanese women were challenged by a dark secondary hyperpigmentation on their faces. The causation of this condition was unknown and incurable till its causative allergens were discovered and cosmetics and soaps which did not contain such allergens were put into production to cure this intractable dermatosis completely. The use of strong allergens had been banned or refrained for some time, but those who were aware of such disastrous allergens retired from the production line of cosmetics when they reached a certain age, only to be replaced by new persons who were unaware of cosmetic allergens and due to this, such allergic diseases have had the chance to come back to become a problem for the female population. This is why the cosmetic allergens of the 20th century as well as the relatively newly discovered ones from the 21st century are currently being reinvestigated along with methods of prevention and therapy through allergen control.

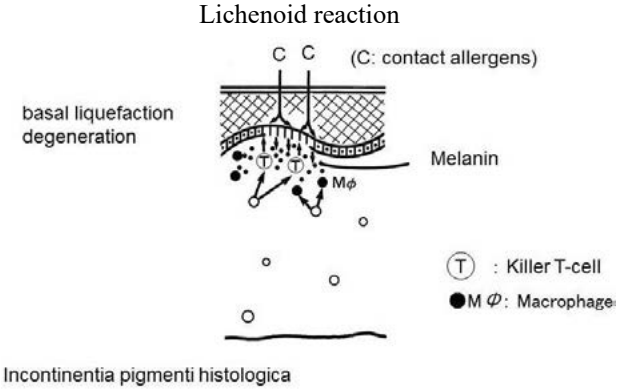
Pigmented cosmetic dermatitis (PCD) in the 1960s and 1970s

There are several kinds of cosmetic dermatitis listed in (**Table 1**). Among them, historically the most disastrous type was the number 3, pigmented cosmetic dermatitis (PCD). Three years after World War II ended and the economic conditions of Japan was getting better, gradually we were noticing more women suffering from acquired dark faces. The disease started without any cause which was subjectively recognized, and the pigmentation started on the face without signs of itchiness or erythema. The configuration of this facial melanosis was either patchy, diffuse or reticular, and normally the effects were only seen on the face. The majority of these cases were women over 15 years of age, and according to the statistics of the author, the average age was 42-years-old. This new disease was reported as melanosis faciei feminae in 1950, and there was no effective treatment including corticosteroid ointments or long term administration of vitamin C [1]. When the author was assigned to the chief dermatologist of the newly organized dermatological allergy clinic in Keio University Hospital, Tokyo, four or five new such melanosis patients visited the section every week, however, there was no remedy to effectively cure the disease.

Table 1: Cosmetic dermatitis

1. Irritant cosmetic dermatitis (Acute, Chronic)
2. Allergic cosmetic dermatitis
3. Pigmented cosmetic dermatitis (old name: Melanosis faciei feminae)
4. Atopic contact dermatitis (Atopic dermatitis + cosmetic dermatitis)
5. Steroid dermatiosis (Steroid rosacea, may complicate demodicidosis)
6. Photodermatitis (Due to musk ambrette, halogenated salicylanilides)

Biopsy of the facial pigmentation showed the presence of liquefaction degeneration of the basal layer of the epidermis, and the invasion of lymphocytes to destroy the basal layer cells. It was a lichenoid reaction accompanying incontinentia pigmenti (**Figure 1**). This fact meant that some allergic reaction must have produced this intractable disease [2, 3].



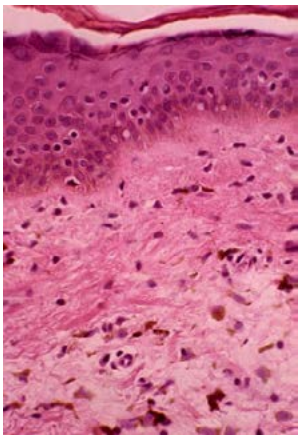


Figure 1: (color) This histopathology of severe case of pigmented cosmetic dermatitis shows marked incontinentia pigmenti histologica and mild invasion of lymphocytes to the basal layer cell of the epidermis.

At that time, the contents of cosmetics were all kept secret, and the letters inquiring the contents of the cosmetics the patients had used were not answered. Some years later, the author was informed that such letters of inquiry were immediately thrown into nearby waste baskets. Therefore, in order to solve this difficult problem, the author visited the Ministry of Health and Welfare to cooperate, by informing the contents of the cosmetics that had been used by the patients from the documents preserved in the Ministry. This cooperation clarified that this facial melanosis occurred by using cosmetics from almost all of the cosmetic companies at that time, and also the contents of mixed fragrances were all secret even to the Ministry of Health and Welfare.

For the next step, the author requested for the cooperation from major fragrance companies, Takasago Perfumery Company and the Pias Company by setting up a research team composed of 32 persons. Among them 10 were dermatologists of Keio University Hospital, 2 were specialisits of statistics, and the others were technicians from these two companies. The purpose of this new research team was firstly to discover cosmetic allergens unknown at that time, and secondly to produce newly designed cosmetics and toiletries which were safe enough for the patients by completely eliminating all the cosmetic allergens for treatment. This new idea was designated as allergen control when the research project started [2, 3, 4]. It can also be called allergen avoidance or allergen elimination or allergen replacement (Calnan). The methods of this investigation are listed in (**Table 2**).

Table 2: Program to Find Out Common Cosmetic Sensitizers and Irritants

1. List of the common cosmetic components (477 species)
2. Measurement of irritation thresholds on 5 healthy individuals (287 species)
3. Confirmative patch test of non-irritating concentrations on 40 healthy individuals
4. Patch test on contact dermatitis patients at non-irritating concentrations
   (a) The nature of the reactions was determined
   allergic or toxic photoallergic or phototoxic
   (b) Cross reactions were examined
   (c) Repeat test (Cronin & Epstein)
   (d) Statistical evaluation
   (e) Effect of allergen control has been observed

A list of all fragrances used for the previous year was provided for research and various kinds of ordinary cosmetic components were collected so that patch tests and photo patch test could be performed from 1969. This was seven years prior to the invention of the Finn Chamber and therefore, in order to patch many kinds of cosmetic ingredients, the Miniplaster which was the smallest patch test plaster in the world at the time was made and put into production. They consisted of six oats of cloth and 7mm in diameter placed on vinyl tape that was 10.2 cm long. By using these small patch test plasters, 48-96 samples could be patch tested at once in order to fulfill the 287 selected cosmetic ingredients out of 477 listed by the research members. About 80% of the samples were fragrant materials and the others were pigments, base materials, bacteriocidals, etc. After the first selection on a few volunteers, 40 healthy volunteers were requested to confirm the non-irritative patch test conditions of all the samples. These cosmetic ingredients were dissolved normally in petrolatum, and those which were not dissolved in petrolatum were dissolved in cream or lanolin for the test.

The patch test was performed for two days, and after the removal of plasters, the reactions were read on the second, third and seventh days under the ICDRG standards. Two identical sets of cosmetic ingredients were patch tested on the right and left sides of the patient's back, and on the second day, ultraviolet rays A at 5.85 J/cm2 were irradiated at the left side only for a photo patch test, lest photo allergy or photo toxicity was overlooked [4].

Results

Many new cosmetic allergens were discovered for the first time through this project which produced pigmented and non-pigmented cosmetic dermatitis. Before this trial, already known cosmetic allergens were eugenol, rose oil, bergamot oil, Balsam of Peru, formaldehyde, coal tar, resorcin, parabens and paraphenylene diamine. By the above mentioned group study, new cosmetic allergens were successively discovered. They were benzyl salicylate, benzyl alcohol, benzyl benzoate, jasmin absolute, isoeugenol, ylangylang oil, cananga oil, cinnamic alcohol, cinnamic

aldehyde, patchouli oil, hay green, sandalwood oil, artificial sandalwood (bornyl methoxy cyclohexanol, BMC), geraniol, geranium oil, orange oil, hydroxycitronellal, methoxycitronellal, oakmoss absolute, armoise oil, yellow No.11 & No.10, red No.31, other phenyl-azo-naphthol group, and vetiver oil.

Costus root oil, methyl heptin carbonate, methyl octine carbonate, α-and β-damascons turned out to be primary sensitizers by the first selection, and consequently the cosmetic industry was requested to stop using them.

As PCD had been an intractable disastrous disease and there were a number of non-pigmented cosmetic dermatitis patients, soon after the discoveries of these new allergens, a project was launched to create and produce cosmetics and toiletries that did not contain any of the cosmetic allergens except for parabens [4]. In this study, paraben allergy turned out to have been so rare that for the majority of patients parabens were considered to be safe to use. On the other hand, the components which produced (2+) or (+) reactions had to be removed completely.

When patch test results were assembled, it turned out that there were many cases of weak positive reactions which showed to be only slightly positive due to erythema and not accompanied by edema or papulovesicular reactions. Such slight reactions occurred due to weak irritants or by allergens when their concentrations were not strong enough to provoke ordinary (2+ or +) reactions. For example, when an essential oil contains small amount of allergic substances, they show minute reactions, or when an allergen could not be dissolved in petrolatum to stay as suspension, similarly a minute reaction is noted. The problem was that when minute reactions appeared, it was not possible to discern weak irritant reactions from weak allergic reactions by the outlook of the patch test results.

When important allergens were overlooked and failed to be eliminated from cosmetics and toiletries, PCD patients were considered not to recover from this intractable disease. With six important components, they were again adjusted to different concentrations or contained in other vehicles to examine whether or not typical allergic reactions were obtained by such alterations. However, such a procedure was not possible with the majority of the 287 cosmetic ingredients tested in this project. Therefore, in evaluating the meaning of minute reactions, statistical evaluation was introduced [5].

(2+) and (+) reactions were given a score of 2, and (-) reactions were given a score of 0, and minute reactions were given the score x (2≥x≥0). Then the value of x which gave minimum error by Fisher's test (F test) was calculated with all the tested samples: when the calculated x was near 2, it meant the minute reaction was considered as an allergic reaction, because the minute reaction deviated significantly to the side of allergic reactions of (2+) or (+). Therefore the material was considered as an allergen, and should not be allowed for cosmetics and toiletries for the cosmetic dermatitis patients' group. On the other hand, when x was 1-0, minute reaction must have been weakly irritative, as it appeared equally in both groups of cosmetic dermatitis and controls. The different equation of calculating x is shown in (**Table 3**), and the calculation was performed by an IBM computer. Two samples were shown with ylangylang oil and benzyl salicylate in the tables 4 and 5, and with both cases, the value of x was 2.0, therefore, in these cases, minute reactions were considered as being allergic (**Table 4 & 5**) [5].

Table 3: Statistical evaluation of weak positive reactions

diseases		number of persons	
		Cosmetic dermatitis	Control group
reactions score			
(2+),(+)	2	a1	a2
?(+)	X	b1	b2
(-)	0	c1	c2
total		d1	d2
average score of group		$\frac{2a_1+b_1x}{d_1}$	$\frac{2a_2+b2x}{d_2}$
average score of total		$\frac{2(a_1+a_2)+(b_1+b_2)x}{d_1+d_2}$	

$2 \geq x \geq 0$

$$f(x)=\frac{1}{\text{distribution rate}} = \text{biological error}$$

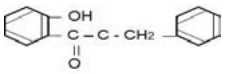
x to make f ' (x) = 0 is adopted to calurate F value of F-test

Table 4: Reactivity of Ylang-ylang oil (5% in petrolatum, evaluated in 1974)

Diseases / Reactions	(1) Cosmetic dermatitis		(2) Controls		Total
	Pigmented	Not pigmented	Pigmented	Not pigmented	
(2+),(+)	9	4	3	0	16
?(+)	10	9	3	0	22
(-)	102	96	112	40	350
Subtotal	121	109	118	40	388
Total	230		158		

Significance between (1) and (2) : F=11.10 ** ,
X^2=2.0 (** P≤0.01, * 0.01<P≤0.05) value of x (?(+)) = 2.0

Table 5: Reactivity of Benzyl salicylate (5% in petrolatum, evaluated in 1974)



Diseases / Reactions	(1) Cosmetic dermatitis		(2) Controls		Total
	Pigmented	Not pigmented	Other dermatitis	Healthy	
(2+),(+)	19	7	1	0	27
?(+)	18	4	3	0	25
(-)	84	98	114	40	336
Subtotal	121	109	118	40	388
Total	230		158		

Significance between (1) and (2) :
F=29.45 ** , X^2=1.6 (** P≤0.01, * 0.01<P≤0.05)
value of x (?(+)) = 2.0

Allergen Control

In 1968, an allergen-free soap by the commercial name of "Minon®" was invented and put into production as a means of therapy towards allergen control so that any patient in Japan could obtain it easily to eliminate all the conceivable contact allergens from soap. The chemical name of Minon® is acyl glutamate and has a pH of 6.0 which is the same as a normal human skin surface. This chemical was selected because tests showed that when alkaline soap of pH 9.5-10.0 is applied, the skin barrier was shown to weaken to absorb various kinds of allergens [6]. Furthermore, the acute and chronic toxicity of acyl glutamate was low enough and the allergenicity (maximization tests) and carcinogenicity was negative. Pigments, fragrances and even parabens were not contained in Minon®.

Allergen-free cosmetics were made two years after Minon® by eliminating all fragrances, phenyl-azo-naphthol group pigments, quinoline yellow group pigments and other lipid / oil sensitizers such as lanolin-derivatives, ricinoleic acid etc. These two combinations of Minon® and allergen-free cosmetics along with cosmetic series patch test allergens already described were together called Allergen Control System (ACS). After a patch test, a treatment system consisting of Minon® and Allergen Controlled Cosmetics without any medications were performed exclusively for PCD patients. Owing to this procedure, PCD which had been incurable for the past 20 years, gradually faded with its dark facial pigmentation. After one year of exclusive usage, their pigmentation had remarkably improved, and on an average of one year and a half, PCD was completely cured. Typical cases are demonstrated in the (**Figures 2 & 3**). The rate of effectiveness in Saiseikai Central Hospital was 146 out of 165 PCD cases (88.5%), and at Watanabe Dermatology Clinic in Shimonoseki, all 53 cases (100%) [3,4]. The latter clinic requested the cooperation of a nearby beauty parlor to use ACS only when PCD patients visited. Fifty PCD patients who were completely cured through ACS indicated a total of 125 cosmetic allergens, proving that there was an average 2.5 cosmetic allergens that produced PCD [3]. This fact showed that usually two or three cosmetic allergens produced PCD and that the complete elimination of pleural cosmetic allergens was the proper treatment. These cosmetics of various kinds had been put into production under the commercial name of "Acseine®" since 1971 by the Pias Company (currently the Acseine Company) so that many PCD patients could be cured.

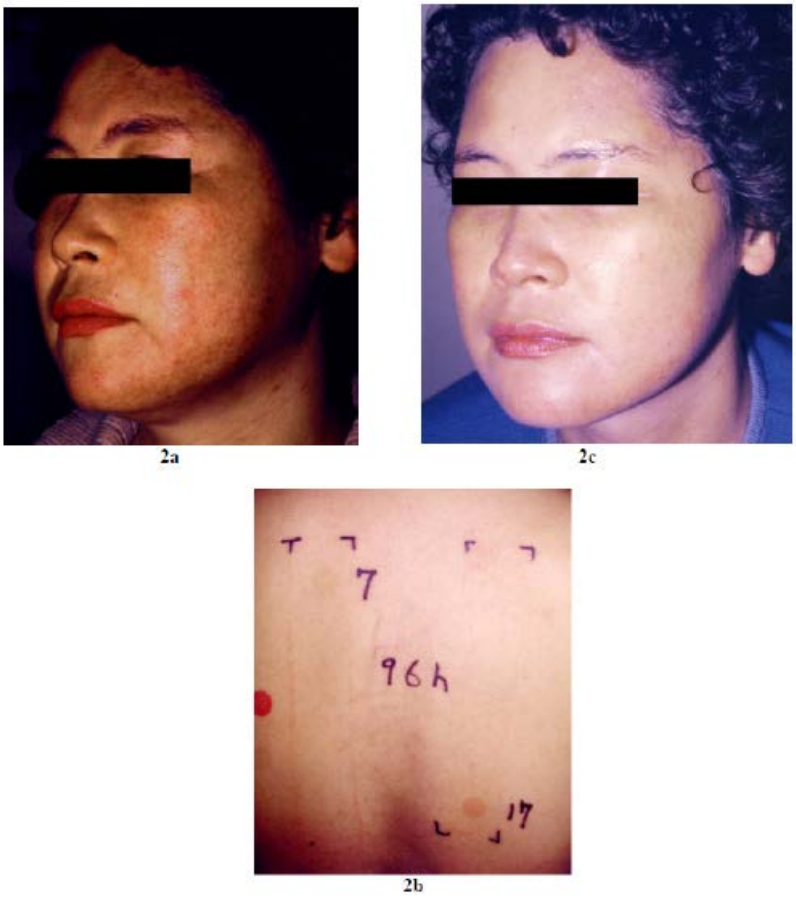


Figure 2: (Color) Pigmented cosmetic dermatitis (PCD) in a 43-year-old woman. Her face had been diffusely dark brown without itching. PCD had been present for the past one year, and antisymptomatic treatment composed of corticosteroid ointment and perorally administered vitamin C did not produce any improvement (2a). Patch test of cosmetic series revealed she was positively sensitized by lithol red AB patch tested at 5% in petrolatum (2b). Exclusive use of Minon® and Acseine® Cosmetics which did not contain such phenyl-azo-naphthol containing pigments cleared PCD completely 3 months later (2c).

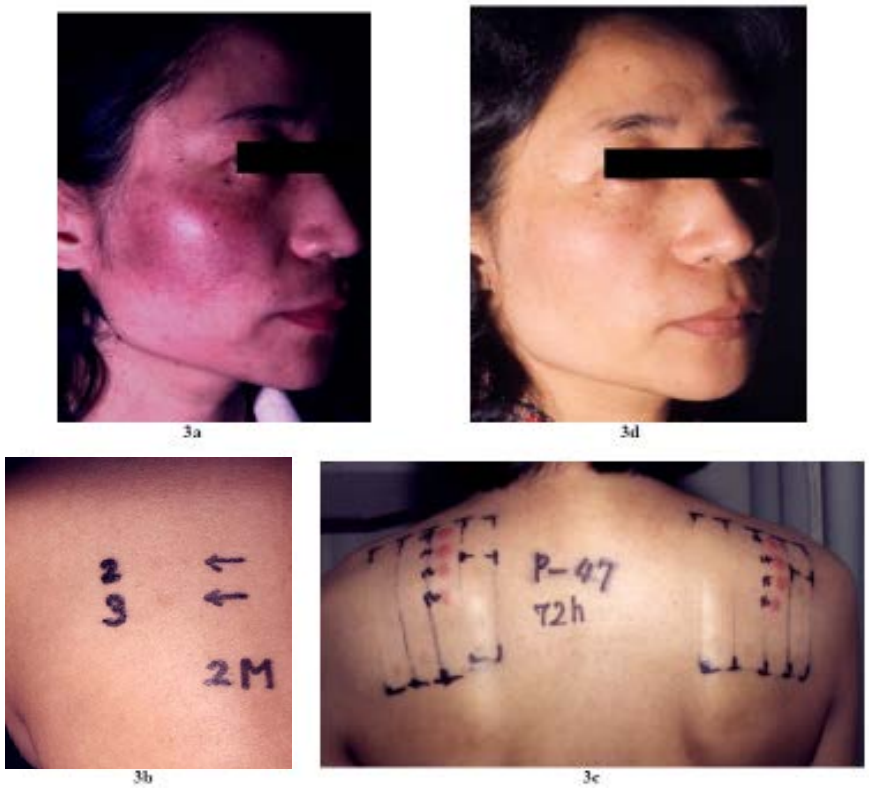


Figure 3: (Color) Pigmented cosmetic dermatitis in a 44-year-old woman who had suffered from severe dark brown pigmentation on the cheeks (3a). Patch test revealed she was positively sensitized by ylangylang oil and cananga oil, which left pale brown pigmentation 2 months after the patch test (3b). 4 years later, such hypersensitivity still remained, and patch test of DCF-3, a main component of ylangylang oil showed strong positive reactions (3c). Her PCD was cured completely by the exclusive usage of Acseine® and Minon® by which she could completely avoided the contact to her cosmetic allergens. 3d shows cure continued after 2 years of 3a.

Thus, PCD, which had been incurable for more than 20 years in the past were cured completely, and not only PCD but also recurrent cosmetic dermatitis (RCD) who repeatedly suffered from facial erythema with itching, and resistant to the usage of corticosteroid ointments, could be cured by the same treatment though the exclusive usage of Minon® and Acseine® cosmetics, because the invasion of common cosmetic allergens were eliminated from the patient's skin (**Figure 4 & 5**). These facts indicate that first most, it is important to perform a cosmetic series patch test and secondly, that the correction of cosmetics and toiletries essential to bring back the normal skin conditions of patients suffering from cosmetic dermatitis [7].

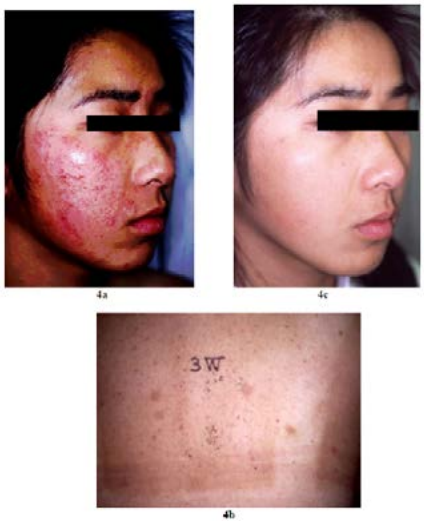


Figure 4: (Color) Recurrent cosmetic dermatitis (RCD) is often seen which cannot be cured by the continual application of corticosteroid ointment (4a). This 24-year-old woman was sensitized by wool alcohol and citronellol derivatives (4b). Exclusiveusage of Acseine® cosmetics and Minon® could get rid of both allergens for her to restore normal skin conditions (4c).

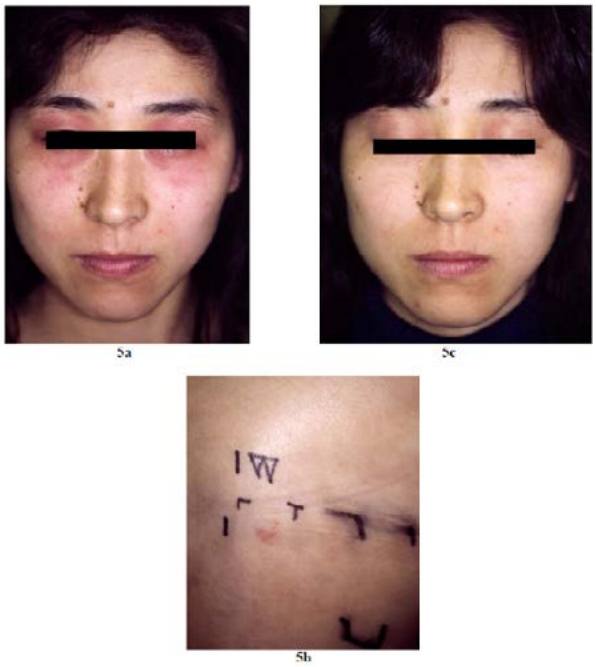


Figure 5: (Color) Recurrent cosmetic dermatitis in a 26-year-old woman. Eyelid dermatitis was severe and itching was severe (5a). Patch test revealed she was positively sensitized by sandalwood oil (SWO) tested at 10% in petrolatum (5b). The exclusive usage of Acseine® cosmetics and Minon® liberated her from the continual contact to SWO to result in complete cure of the disease (5c).

Chemical-induced SLE due quinolin yellow pigments

As byproduct of ACS, systemic lupus erythematodes (SLE) provoked by a cosmetic component was discovered in 1979 by Inamoto [8]. The symptoms of this SLE were a persistent butterfly-shaped erythema of the face with slight or moderate itching, cheilitis, positive serum antinucleic antibody (ANA) at 320-160 times serum dilution, hypergammaglobulinemia and occasional mild leukocytopenia (**Figure 6**). Fever, myalgia, arthralgia, defluvium and renal damage were not present, therefore, it was similar to a drug-induced SLE. Patch test of 5% or 1% D&C Yellow No.11 (Japanese name Yellow 204) in polyethyleneglycol (PEG) was clearly positive, and one case showed flare of systemic erythema with fever after its positive patch test [9]. Calnan similarly reported a flare of systemic erythema after its patch test in his reported case [10].

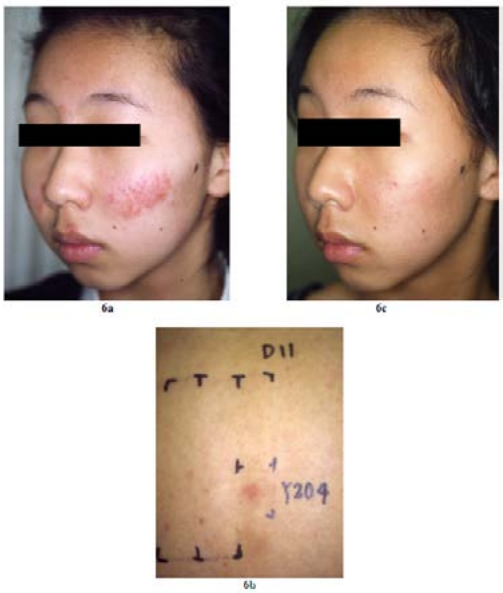
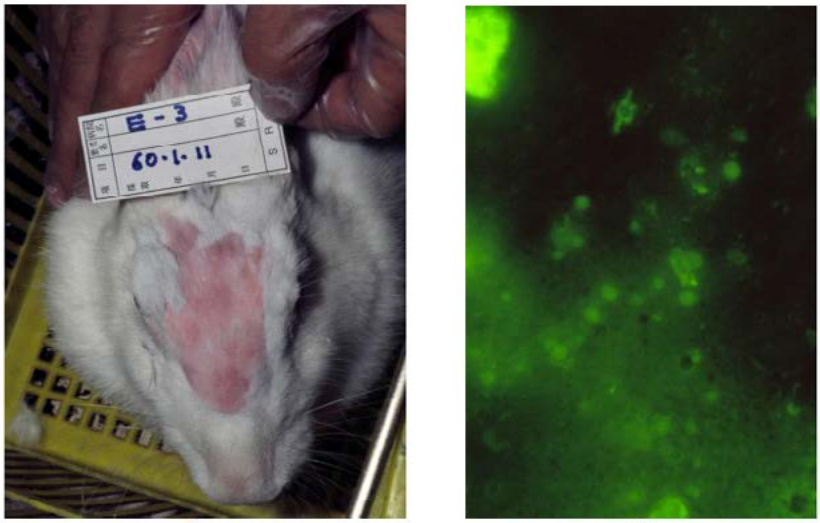


Figure 6: (Color) A case of SLE in a 17-year-old female. She had suffered from a butterfly shaped erythema with slight itching since a year previous. As serum ANA was 160 times dilution positive, her doctor prescribed low dosis of prednisolne with no effect (6a). Patch test revealed strong positive reaction to 1% Yellow No.11 (Japanese name: Y-204) in PEG which remained still positive on the 11th day of the patch test (6b). No other abnormalities were found. Exclusive usage of Acseine® cosmetics and Minon® completely eliminated Yellow No.11 from her contact environment, and she was cured completely 6 months later (6c). She was followed up for 8 years without relapse, and serum ANA became negative.

At the request of the Consumers' Department, City of Tokyo, an animal test was performed in 1985 to show whether or not the sensitization of D&C Yellow No.11 produces experimental SLE among rabbits. In this experiment, Yellow No.11 was injected subcutaneously at 1mg a week with 1mg DNA (calf thymus) and 0.5ml of Freund's complete adjuvant (FCA). Two months later, generalized edematous erythema appeared on all five rabbits, and intra cutaneous test of 0.1% Yellow No.11 PEG at 0.1ml was negative at first, but became positive with marked erythema and edema one month into the experiment. Nine weeks into the experiment, two out of three rabbits that continued to have injections showed positive ANA, and one showed positive at 80 times serum dilution (Figure 7), and another showed a peripheral pattern reaction. These results certified that Yellow No.11 sensitized rabbits at 100%, and that serum ANA became positive by its sensitization. ANA was negative with all other controled rabbits that did not have Yellow No.11, but only had injections of DNA plus FCA. Seeing several reports on these, the Department of Health and Welfare of Japan prohibited the usage of two strong primary sensitizers, D&C Yellow No.11 and D&C Red 31 to ordinary cosmetics and toiletries, and their partial prohibition was followed by the EU and USA [11].



7a 7b

Figure 7: (Color) Sensitization by subcutaneous injection of 1% Yellow No.11 PEG with DNA and FCA every week produced edematous erythema on many areas of rabbits (7a). In one rabbit, serum ANA became positive at 80 times dilution positive (7b), and in another rabbit a peripheral pattern was positive. The rate of conjugation of Yellow No.11 and DNA was only 1%, however it easily sensitized 5 rabbits at 100%, and produced such ANA.

This type of SLE was also cured by the exclusive usage of ACS, because the invasion of Yellow No.11 was completely blocked by ACS (Figure 6). This unique type of SLE was considered as a type of drug-induced SLE, or better called the "chemical-induced SLE". After the inhibition of Yellow No.11, cases like Fig6 seem to have gradually decreased, but have not yet disappeared completely. Yellow No.10, which is four sulfurate of Yellow No.11, and contains Yellow No.11 as an impurity at maximum 20% is watersoluble, and is still being used around the world.

Reseach to find out safely used cosmetic components

In the later part of this research, new cosmetic allergens continued to be discovered, and at the same time, cosmetic components which were not sensitizers non irritants were also looked for, in order to make cosmetics as safe as possible. Due to the fact that cosmetic industries were present in many countries, the cooperation of dermatologists who investigated cosmetic allergens in seven countries was requested. Using the same method, USA, Germany, UK, Sweden, Switzerland and Denmark joined the original teams of Japan. In one year when a certain country could not join, Ireland replaced the position [12,13]. The author would personally like to thank the efforts or their sincere cooperation. As there were almost 6,000 fragrant materials, and considering that the majority of new cosmetic allergens discovered in the first part were fragrances except for several pigments and oils, again a number of fragrances were evaluated as to their allergenicity using the same method. Finn Chambers were adopted at this time. The results showed that the discovery of new cosmetic allergens in this later project was not so many as before, and rather that cosmetic components which were not sensitizers non irritants were found. This was definitely good information that helped make cosmetics safer.

To find out causative allergens for the patients, Larsen invented a mixed fragrance reagents to detect cosmetic allergy by a single patch test. Fragrance mix No.1 contained hydroxycitronellal, eugenol, isoeugenol, geraniol, cinnamic alcohol, cinnamic aldehyde, α-amylcinnamic aldehyde, and oakmoss absolute each at 1% in a total of 8% in petrolatum, and have been used widely around the world. Fragrance mix No2. contained jasmin absolute, ylangylang oil, narcissos absolute, sandalwood oil and spearmint oil each at 2% or 1% in a total of 8% in petrolatum [12,13]. By the combined usage of these two Fragrance mixtures and 25% Balsam of Peru, 95% of fragrance allergy could be demonstrated. It was a progress in diagnosing a variety of fragrance allergens [12,13]. The record of this study accumnulated for 18 years during the 20th Century enabled to classify the allergenicity of fragrances into four categories, Class A: Common sensitizers, Class B: Rare sensitizers, Class C: not sensitizing but showed slight irritancy by patch test on both the cosmetic dermatitis group and control group, Class D: not sensitizing and not irritating (**Table 6 & 7**) [7,11]. The

typical reaction of Class D is demonstrated in (**Table 8**). Primary sensitizers were recommended to be not used, and Class A and B should not be used at higher concentrations. Class C and D were considered to be safe to use. The results were published so that the Research Institute of Fragrant Materials (RIFM) can be aware of the data to cooperate in order to reduce cosmetic dermatitis. These data are precious to reduce cosmetic dermatitis, however, considering the fact that the literature published in 1998 [7,11] is already difficult to obtain, they have been reported once again in [7,11] (**Table 7**).

Class	Fragrances
A	Common sensitizers
B	Rare sensitizers
C	Almost non-sensitizing, Slightly irritative
D	Never sensitizerd, Not irritative

Table 6: Basis of the Investigation

1. Rose oil, lavender oil, eugenol, bergamot oil, etc. were described to have been contact sensitizers in the acclaimed textbook "Contact Dermatitis (First edition)" by Dr. Alexander A. Fisher in 1967.
2 A number of new fragrance contact sensitizers were discovered during 1970-1974 in Japan for the solution of pigmented cosmetic dermatitis (Allergen Control System).
3. Confirmation studies followed in many countries.
4. Substitutes to common fragrance contact sensitizers were found during 1985-1987 in Japan (The Project E-300). Substitutes were called Class C and D fragrances.

Table7: Class A, B, C, D of fragrances

Class A fragrances (common cosmetic sensitizers and primary sensitizers)	
Hydroxycitronellal (d&d,l)	Geranium oil
Jasmine absolute	Sandalwood oil
Ylang-ylang oil	Artificial sandalwood
Cananga oil	(Bornyl methoxy cyclohexanol containing artificial sandalwood)
Cinnamic alcohol	Hay green
Cinnamic aldehyde	Musk ambrette
Eugenol	Armoise oil
Isoeugenol	Narucissus absolute
Benzyl salicylate	Lavender oil
Balsam of Peru	Bay oil
d-Carvone	Violet leaves absolute
l-Carvone	Methylheptine carbonate
Costus root oil	Methyloctine carbonate
α-Damascone	β-Damascone
Geraniol	
Class B fragrances (rare sensitizers)	
Amylis oil	Fir balsam absolute
Citral diethyl acetate	Nutmeg oil
l-Hydroxycitronellal	d-Methoxycitronellal
Vetiver oil	cis-3-Hexenyl acetate
α-Ionone	Acetivenol
β-Ionone	Allyl cyclohexyl propionate
Methylisoeugenol	Bourgenons de cassis absolute
Clove buds oil	β-Damacenone
Cedarwood oil	5-Cyclohexadecenone
Basil oil	Rose de May absolute
Cedramber	γ-Methylionone
Oakmoss absolute	α-Methylionone
Petitgrain citronnier	Others
Iso E super	
Class C Fragrances (virtually nonesnsitizing fragrances)	
Isoamyl salicylate	Gerany nitril
γ-Dodecalactone	Lyral
Guaiacyl acetate	Musk tibetene
6-Isobutyl quinoline	Ligustral
γ-Undecalactone	ε-Nonalactone

Neroli oil	Rosemary oil
Bergamot oil FL (furocoumarinfree)	p-tert-Butyl cyclohexyl acetate
Tetrahydrogeraniol	Allyl amyl glycolate
ε-Decalactone	Allyl ionone
cis-3-Hexenol	Ambrette seed oil
Musk ketone	Bois de rose oil
Citral hexylene glycol acetal	Linalool
Caraway oil	Mentyl acetate
Citronellyl acetate	Petigrain oil
Cumin oil	l-Nonanal
l-Methoxycitronellal	l-Decanal
Isobutyl salicylate	Bacdanol
Phenyl propyl alcohol	Others
Lavandin oil	
Class D fragrances (considered as nonsensitizers)	
Linalool oxide	ε-Dodecalactone
Dihydro linalool	Phenylethyl isoamyl ether
Dihydro myrcenol	Mandarin oil
Myrcenyl acetate	Octyl dodecanol
Pentalide	Almond oil
Phenylethyl salicylate	Phenylacetaldehyde dimethylacetal
Tonka absolute	Jasmal
Tetrahydro linalool	δ-Nonalactone
Tetrahydromuguol	δ-Undecalactone
Tetrahydromyrcenol	γ-Nonalactone
Isopropyl myristate	γ-Decalactone
Hedione	δ-Dodecalactone
Citronellyl nitrile	Isobuthyl angelate
Lemon FL (furocoumarinfree)	cis-3-Hexenyl salicylate
Lime oil FL (furocoumarinfree)	Others

Table 8 Typical patch test reaction of a class D fragrance

Diseases / Reactions	(1) Cosmetic dermatitis		(2) Controls		Total
	Pigmented	Not pigmented	Pigmented	Not pigmented	
(2+),(+)	0	0	0	0	0
?(+)	0	0	0	0	0
(-)	25	58	61	40	184
Subtotal	25	58	61	40	184
Total	83		101		

Significance between (1) and (2) :
F=0.0, X^2=0.0 (** P≤0.01, * 0.01<P≤0.05)
value of x (?(+)) = 0

Improvement of Allergens

Among Class A fragrances, there were two valuable and precious essential oils which had a history of more than 300 years of usage. They have been known to have such an exquisite scent that strongly attracts men when they were used by women. They were considered as precious civilization, and therefore two researches started in the second part of this study. These fragrances were ylangylang oil and jasmin absolute.

Firstly, ylangylang oil was analyzed by Mass-Gas Chromatography Spectrometry, then its two or three components were fractionated and patch tested again on those who were hypersensitive to ylangylang oil. The results revealed that it was dehydrodiisoeugenol (DDIE) that were the true allergen in ylangylang oil. All other components showed negative patch test results (**Figure 8**). DDIE was applied on the razed backs of five guinea pigs everyday, it produced eczema on all five guinea pigs to clearly demonstrate that there was a real contact sensitizer in ylangylang oil. As DDIE belonged to high boiling point components, it could be successfully removed by distillation during production.

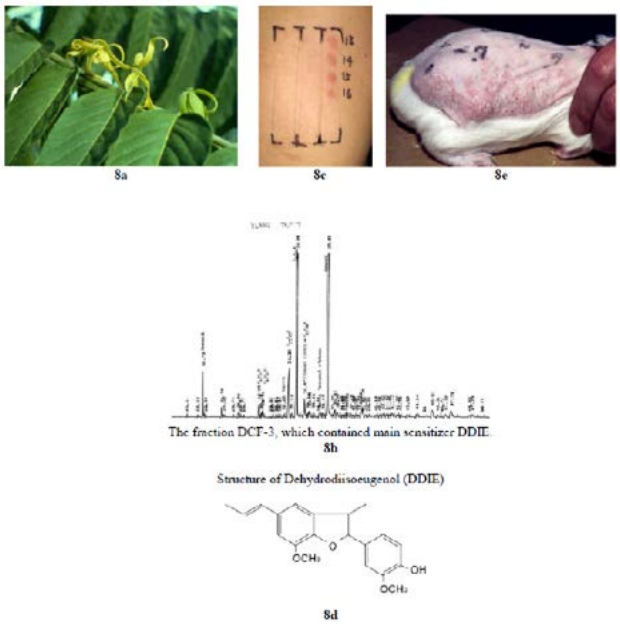


Figure 8: (Color) Ylangylang oil, which strongly attracts men to women when they wear it, is extracted from the flower of ylangylang (8a). It is a common cosmetic sensitizer, and when fractionated components were patch tested on those who have allergy to it, the fraction DCF-3 (8b) was apparently the responsible sensitizer (8c). Precise study on this fraction revealed that dehydrodiisoeugenol (DDIE) turned out to be the main sensitizer (8d), which could produce severe eczema on all 5 guinea pigs by a daily simple application on the back (8e).

As for jasmin absolute, among its more than 100 components, the main components such as benzyl groups (benzyl acetate, benzyl benzoate, benzyl alcohol, benzyl cyanide), cis-jasmone, d-linalool, geraniol, geranil-linalool, α-terpineol, nerol, farnesol, eugenol, benzaldehyde turned out to have been not responsible for jasmins allergy through patch testing, even though some of them are cross reacting sensitzers. Therefore, the most excellent perfumer, Hitoshi Hiroyama of the Hasegawa Perfumery Company, Tokyo was requested to make an "artificial jasmin" using only Class C and D fragrances. When each 10% natural jasmin absolute and artificial jasmin of Hiroyama in petrolatum were patch tested on 178 cosmetic dermatitis patients among seven countries, the positive rate of natural jasmin absolute was 30 among 178 (16.9%). On the other hand, the artificial jasmine Hiroyama was 0 among the same 178 patients, even though the scent of the two fragrances seemed to be quite similar by the evaluation of the participating dermatologists and engineers. This fact meant that artificial jasmin made of Class C and D fragrances can be expected to be used safely avoiding cosmetic dermatitis (**Table 9**). The positive rates of cosmetic allergens using cosmetic series allergens did drop down to the levels of 5% -8% near the end of the 20th century but currently have not become completely eradicated.

Table 9: The Reactivities of Natural Jasmin Absolute and Hypoallergenic Artificial Jasmin at 10% in Petrolatum in 178 cosmetic dermatitis patients in 7 Countries.

	Positive	Negative
Natural Jasmin Absolute	30 (16.9%)	148
Hypoallergenic Artificial Jamin* (Hiroyama)	0	178

*Made of Class C and D fragrances only.

Metal allergens became the top scoring positive rate of patch test with cosmetic dermatitis patients in the 21st Century

In this current millennium, the positive rates among cosmetic dermatitis patients have been followed up on. In the table 10, the reactivities of each cosmetic allergens in the years 2011-2015 are demonstrated (**Table 10**). In this table it is recognized that those classical allergens in the 20th Century still remain, keeping the rates around 5% to 8%.

Table 10: Results of Cosmetic Series Patch Test Allergens in the patients with Pigmented Cosmetic Dermatitis (Melanosis faciei feminae) and Recurrent Cosmetic Dermatitis (C-26) (Years: 2011 - 2015).

No.	Allergens	%	Base	Positive	Positive rate (%)	n
1	Fragrance mix No.1	1% of 8 species (8%)	Pet.	57	8.7	657
2	Fragrance mix No.2	2%-1% of 5 species(8%)	Pet.	29	4.4	657
3	Balsam peru	25	Pet.	22	3.3	657
4	Methl Paraben	3	Pet.	11	1.7	657
5	PAN	0.05	Pet.	27	4.1	657
6	Wool Alcohol	30	Pet.	4	0.6	657

7	Ricinoleic acid	10	lanolin	13	2.0	657
8	P.P.D.A.	1	Pet.	51	7.8	657
9	$NiSO_4$	2.5	Pet.	134	20.4	657
10	$K_2Cr_2O_7$	0.5	Pet.	50	7.6	657
11	Benzyl salicylate	5	Pet.	15	2.3	657
12	Oxybenzone	2	Aq.	3	0.5	657
13	Pyrogallol	1	Pet.	5	0.8	657
14	Lanolin	as is	Pet.	3	0.5	657
15	C			3	0.5	657
16	Plaster dermatitis			0	0.0	657

PAN : Phenyl-azo-2-naphthol
Pet : Petrolatum

PPDA : Paraphenylene diamine
Aq. : Purified water

	n	average age
Male	21	53.4
Female	636	45.6
Total	657	45.8

On the other hand, 2.5% $NiSO_4$ in petrolatum showed the highest figure of 20.4% among 657 cosmetic dermatitis patients. This tendency started the turn of the century and still remains. Similar results were reported by Deguchi in 2016. In the report, the positive rate of $NiSO_4$ was 21.2% among 71 rosacea-like facial dermatitis patients composed of one male and 70 females [14]. When various metal allergy in recent cosmetic dermatitis patients in 2010 was investigated, results showed that not only nickel but also chromate, stannic, mercury, cobalt, platinum, moribudenum, manganese and copper were the contact allergens detected (**Table 11**) [15].

Table 11: Metal allergy in cosmetic dermatitis patients

No.	Metals	%	Base	(2+),(+)	?(+)	(-)	n	Positive rates (%)
1	$CuSO_4$	2	Aq.	6	9	75	90	6.7
2	$PdCl_2$	1	Aq.	4	2	84	90	4.4
3	$K_2Cr_2O_7$	0.4	Aq.	11	18	61	90	12.2
4	$NiSO_4$	5	Aq.	47	9	34	90	52.2
5	"	2	Aq.	25	7	58	90	27.8
6	$CoCl_2$	2	Aq.	18	13	59	90	20.0
7	$HgCl_2$	0.1	Aq.	29	15	46	90	32.2
8	"	0.05	Aq.	13	15	62	90	14.4
9	$SnCl_4$	1	Aq.	30	18	42	90	33.3
10	$CdSO_4$	1	Aq.	4	7	79	90	4.4
11	$HAuCl_4$	0.2	Aq.	4	3	83	90	4.4
12	H_2PtCl_6	0.5	Aq.	19	33	38	90	21.1
13	$FeCl_3$	2	Aq.	1	8	81	90	1.1
14	$InCl_3$	1	Aq.	1	5	84	90	1.1
15	$IrCl_4$	1	Aq.	1	4	85	90	1.1
16	$MoCl_5$	1	Aq.	9	14	67	90	10.0
17	AgBr	2	Pet.	0	1	89	90	0.0
18	$SbCl_3$	1	Pet.	1	0	89	90	1.1
19	$ZnCl_2$	2	Pet.	3	1	86	90	3.3
20	$MnCl_2$	2	Pet.	9	3	78	90	10.0
21	Plaster dermatitis			8	0	82	90	8.9

ICDRG standards
2+, + : positive
?+, - : negative

	n	average age
Male	1	32.0
Female	89	40.6
Total	90	40.5

Allergy to these metal ions was not produced by cosmetics primarily in most cases, but presumed to be produced by ear piercing at high teen ages, and naturally it remained for many years to be provoked by a small amount of metal ions in their cosmetics [16]. (**Table 12**) shows the results of metal analysis in cosmetics and cosmetics instruments, revealing the presence of various metal allergens [15].

Table 12: Results of metal analysis

Cosmetic instruments and containers	
(1) Eyelash curler (eyelash curler)	5
(2) Tweezers	2
(3) Containers and frames	20
Total	27

Elements detected : 25 species

Ni, Co, Cr, Cu, Pd, Au, Mn, Zn, Fe, Mo, Ga, Zr, Br, Bi, Ti, Al, Si, Ca, K, S, Cl, Nb, Ba, Y, V

Ni	≥1%	7	15
	0.1%>	8	
Co	≥1%	2	10
	0.1%>	8	
Cr	≥1%	2	6
	0.1%>	4	
Cu	≥1%	7	19
	0.1%>	12	
Au	0.1%>	12	12

	Cosmetics	
a	Eye shadow	14
b	Foundation	11
c	Powder	4
d	Cream & lotion	4
e	Mascara, eyeliner and core of eye pencil	3
f	Remover	3
	Total	39

Metals detected: 25 species

Allergens: Ni, Co, Cr, Cu, Pd, Au, Zn, Mn Others: Fe, Ga, Zr, Rb, Bi, Ti, Al, Si, Ca, K, S, Cl, Nb, Sr, Ba, Y, V

Ni	≥1%	1	15
	0.9-0.1%	6	
	0.1%>	8	
Co	≥1%	1	4
	0.9-0.1%	2	
	0.1%>	1	
Cr	≥1%	2	12
	0.9-0.1%	2	
	0.1%>	8	
Cu	≥1%	2	9
	0.9-0.1%	4	
	0.1%>	3	
Au*	0.1%>	3	3

* Gold lotion, Gold cream

It is understandable that metal allergens were detected from cosmetic instruments, such as eyelash curlers, dishes of foundations and

other parts of the containers. The highest concentration of nickel was 80% with one case of an eyelash curler. Whereas with lotions and creams, metal ions are supplied from metal blades for mixing for a long time or from metal containers before production. With sunscreen creams or lotions, analysis revealed that the presence of nickel from the stainless stirring ball in the cosmetics, and five patients were cured of facial dermatitis after they stopped the usage of the metal ball containing sun screen creams, as they were hypersensitive to nickel. A case of cosmetic dermatitis due to metal ions from cosmetics is demonstrated in (**Figure 9**). Other new cosmetic allergen, rhododenol, a whitening agent, and glupal AS, a wheat protein produced many dermatitis patients in Japan in the 21st Century [17,18,19]. Since they were proven to be strongly allergenic, they will never be used. Generally speaking, food protein should not be used for cosmetic and toiletries, because once it sensitizes, the disaster is serious and long lasting. Food is for eating, and not for cosmetics.

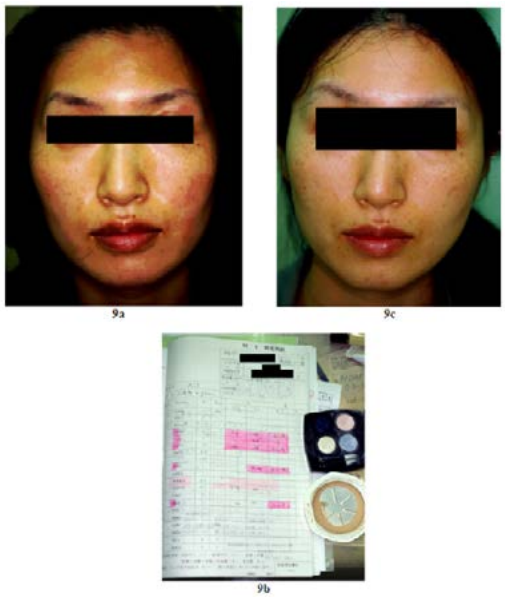


Figure 9: (Color) A 30-year-old woman suffered from facial erythema with itching. As the dermatitis had been recurrent (9a), a patch test was performed to reveal the presence of nickel allergy, as is indicated in red on the record paper (9b). Such metal plates of the foundation contained nickel at 2.5% by analysis, therefore, she was requested to change foundations which were in a plastic plate, for the avoidance of nickel. By this avoidance, her dermatitis disappeared (9c).

Conclusion

Hereafter in order to reduce allergic recurrent cosmetic dermatitis, firstly the classic cosmetic allergens of Class A should be replaced to Class C and D fragrances. Primary sensitizers such as D & C Yellow No.11 and D & C Red No.31 should remain prohibited. Metal instruments, containers and mixing balls should be replaced to non-metal materials whenever possible. However, Almite, on aluminum covered by oxidized aluminum membrane and pure titanium can be safely used. In conclusion, allergen free cosmetics and soaps such as Acseine® and Minon® should continue to be produced as they can be safely applied and will bring back healthy facial skin conditions to those suffering [16]. Stats from the year 2010 indicate that new people with mild PCD cases can often regress because cosmetics can be altered due to generational changes and history often repeating itself [4].

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