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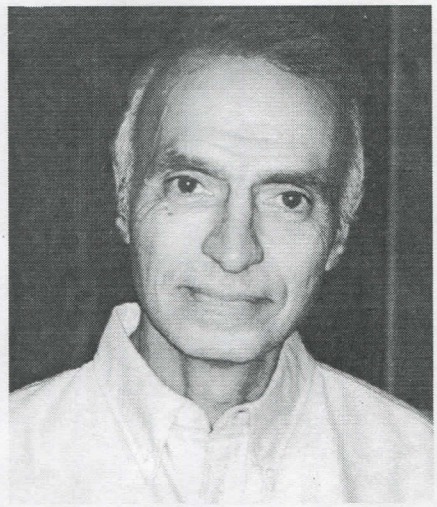

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by Dr. Omar M. Amin, PhD

Abstract: Neurocutaneous syndrome (NCS), a newly discovered toxicity disorder, is described in light of our new understanding of its relationships with the causative agents included in the dental liners used in afflicted patients. NCS is characterized by neurological sensations, pain, depleted energy and memory loss as well as itchy cutaneous lesions that may invite various opportunistic infections. Components in the calcium hydroxide dental sealants Dycal, Life and Sealapex have been identified as sources of the observed symptoms considered compatible with classical sulfa toxicity. Sulfonamide and neurological toxicity issues are discussed, three case histories are presented and an outline of management protocol is proposed. Additional notes on zinc oxide, Fynal, IRM and Sultan U/P sealants are also included.

Introduction

The original description of the neurocutaneous syndrome(NCS)[1] was "introductory in nature... intended only to bring attention to a new disease entity that has not been previously reported."[1]

Examination of many NCS patients and a careful study of their symptoms, exposures, clinical conditions and histories have made it possible to identify the underlying cause of the syndrome and proceed with its management. It is now also possible to help NCS clinical cases and to make dentists aware of the adverse impact of some routine dental procedures commonly regarded as harmless or safe.

Materials and Methods

NCS patients from the United States sought our help after having exhausted all other means to resolve their symptoms. Upon signing an informed consent, patients were personally evaluated and their clinical history, records, symptomology and exposures carefully examined. Fecal and blood specimens provided or collected at the Parasitology Center, Inc. (PCI) were studied and identified. An NCS status was only determined upon confirming that neurological and dermatological symptoms are compatible with those of NCS and that one or more of the suspect sealants (based on the dental records of hundreds of patients) have been used on prior dates. Sensitivity to sulfa and the level of sulfa in the blood were used as a confirmation of sulfonamide toxicity. Continuing patients followed our recommendations of rehabilitation of their compromised teeth, removed suspect liner(s), and replaced with ethyltoluene sulfonomide (ETS)- and zinc oxide-free sealers. We provided the dentists with a list of vitamin/mineral supplements for the patient to take during the transitional period and another list of substitute sealants. Patients were followed up for weeks/months to monitor the resolution of all symptoms.

Results and Discussion

The Neurocutaneous Syndrome

The disorder is a double faceted condition, dermatological and neurological, with clear-cut symptoms of classical sulfa toxicity. The latter is characterized by abnormal blood and bacterial flora values, photosensitive reactions, allergic vasculitis sores,and redness of the skin,

which may lead to liver and kidney failure.[2] The neurological aspects of NCS are characterized by pin-prick and/or creeping, painful and irritating movement sensations, often interpreted as parasite movements subcutaneously or in various body tissues or cavities including the head. In the latter case, movement sensations are either unipolar or bipolar and may proceed horizontally or vertically. They may manifest as readily observable variably shaped bruises or waves of elevated ripples or channels. In no case was the movement sensation related to parasites which were always found absent.[1] Neurological symptoms may also include loss of memory, brain fog, lack of concentration and control of voluntary movements.

The cutaneous aspects include small itchy sores (Fig.1), inflamed often elevated pimples (Figs.2,3) and painful and fully open/ amorphous mucoid lesions that often enlarge and coalese (Fig.4). Histopathological sections of lesions (Fig.5) in nine biopsied patients show superficial and deep perivascular infiltrate of lymphocytes, accompanied by interstitial deposits of granular mucin material. Eosonophils are usually present within the inflammatory infiltrate and foci of epidermolytic hypokeratosis are often identified within the epidermis (Fig.5). Lesions may also be on the scalp where they may be associated with infestation of springtails (Collembola).[1] In many cases, lesions are associated with edematous reactions usually in the arms and legs (Fig.6). Blood vessels may also become enlarged and elevated, and the head may become hot and turn red. The gum tissue and the teeth may turn gray and become compromised first and stay compromised the longest. Mucoid secretions from gum and other tissues may also turn gray. No parasites were ever detected from these, or any other compromised sites.[1] The above creeping sensation is clearly distinguished from these caused by nematodes such as Toxocara canis[3] or Dioctophyme sp.[4]

General symptoms usually include fatigue, compromised immune system and psychological trauma. Elevated sulfa levels are also observed in the blood of tested patients. The depressed immune status pre-empts the patient for opportunistic infections.

Compounding Factors

While NCS itself is not a contagious condition, superimposed opportunistic infections on open sores may be. Initial infection with fungus or bacteria appear to attract subsequent infestations with many arthropod species, especially springtails (Collembola: Insecta).[1,5,6,7] Black specks associated with such infections appear to be metabolic waste (fecal elements) of these organisms or mycelial masses of certain fungal species. Staphylococci, e.g., Staphylococcus aureus and S. haemolyticus; actinomycetes, e.g., Streptomyces spp.; and yeast, e.g., Candida albicans; Mycetomas, e.g., Madurella spp. among others, have been identified from cultured swabs taken from sores of various NCS patients. Opportunistic infections with these organisms have been shown to aggrevate the cutaneous symptoms of NCS patients.[8] The black grains of the mycelial masses of Madurella spp. may be related to the "black specks" often reported by NCS patients. Treatment of these sores may resolve the superimposed infection but does not affect the NCS condition.

Arthropods identified from sores include fleas (Siphonaptera), caterpillars (Lepidoptera), wasps and ants (Hymenoptra), beetles (Coleoptera), winged flies and midges (Diptera), thrips (Thysanoptera), ticks, mites and spiders (Arachnida) and springtails (Collembola).[1,4] While springtails have close association with sores in many NCS patients, it should be emphasized that they, and other opportunistic infections represent aggravating but not causal factors of NCS sores.

Unidentifiable filaments (non-textile fibers)

have also been observed in many NCS patients associated with lesions and may be related to the mycelia of Madurella spp. The healing of certain patients lesions,[9] however, was observed to be proportional to the exit of remaining fibers from lesions[3]. Patients experiencing complete remission remain susceptible to fungal promoting conditions in damp, shaded, moldy places.

The Sealants

The three major calcium hydroxide sealants causing NCS (Dycal, Life and Sealapex) are considered in this study[9]. While promoted as calcium hydroxide sealants, they only include about 50% calcium hydroxide in the catalyst. Other components that are identical in all three sealants (Table1) are scarcely known or advertised but will, however, impact the patient in the same manner.

Of the components common to all three sealants, ethyltoluene sulfonamide as well as zinc oxide are considered most toxic. Toluene is a known potent nerve toxin[10] associated with the neurological symptoms of NCS. The sulfonamide component of this compound brings about a sensitivity allergic-toxic reaction ultimately manifesting as the vascular mucoid sores characteristic of the NCS, especially in sulfa sensitive patients.

Zinc oxide was shown to be genotoxic[11], cytotoxic[12,13], killing macrophages[14], and causing chronic and fibrous inflammatory reactions,[15,16] ulcerations[16] and osteosclerosis.[17] Additionally, the toxic effects of zinc oxide and calcium hydroxide were shown to be similar.[18,19] Calcium hydroxide was shown to cause periapical inflammation, typical granuloma and partial lack of healing.[20] Titanium dioxide and Barium ions (Table 1) were also shown to provoke strong foreign body and bio-incompatible reactions in live tissue.[21,22]

We observed that the toxicity of ethyltoluene sulfonamide is determined by the concentration of this compound in the sealant used, the amount of sealant used and the number of teeth involved. The patient's reaction will depend on the degree of sensitivity to the compounds. These variables determine the time after which the patient will begin to experience symptoms. This time was observed to vary between one day and many years after the original dental procedure. Neurological and cutaneous symptoms are not necessarily similar in intensity and the pathology of sores varied between unremarkable to extremely overt but the neurological sensations were usually severe especially at night.

Cytotoxicity of Dycal, Life and Sealapex was clearly demonstrated invivo and invitro in various tissues.[23] Sealapex was shown to cause severe inflammatory infiltration[15,24,25] and edema[25] accompanied by subcutaneous tissue necrosis[15,26] and progressive differentiation and reaction of monocytes, macrophages and epithelial cells[27]. The final phase of the inflammation is characterized by an intense granulomatous reaction especially in epithelial cells causing various intensities of irritation.[28] The cytotoxicity[29,30] and neurotoxicity[31] of Sealapex was well demonstrated in various mammalian systems.

As with Sealapex, Dycal was also shown to cause hemorrhage and acute to consistent inflammatory cell[16,32,33] necrosis,[16,32,33] tissue loss,[33] karyorrhexis,[16] neurotoxicity.[34] and formation of serous exudates.[16] Life has been the least researched sealant. It, however, has the same toxic ingredients, i.e., ethyltoleune sulfonamide and zinc oxide, as Sealapex and Dycal and has been associated with classical NCS symptoms in some of our patients, e.g., DB (Fig.6) and MM (Fig.4).

Sealants not containing ethyltoluene sulfonamide but including zinc oxide and eugenol have also been associated with NCS cases.These include Fynal(>75% zinc oxide), IRM and Sultan U/P(<50% zinc oxide). Fynal was associated with the cases of MM (Fig.4), and among other cases not discussed here. Fynal has been classified as "hazardous" in the manufacturer's (Dentsply caulk) material safety data sheet (MSDS) causing "redness and irritation" upon skin contact and "open sores or wounds of the skin" in persons with known sensitization to eugenol. Similarly, IRM (by Dentsply caulk) and Sultan U/P(by Sultan Chemists) were associated with a classical NCS case in TS, a 30-year-old white female. Of 19 teeth, which had dental work performed between 1995-1996, 5 were sealed with IRM (3) and Sultan U/P(2). In the other 14 teeth, Gluma One Bond (by Heraeus Kulzer) and Scotch bond (by 3M) were used. The latter two products contain 2-hydroxyethyl methacrylate and the MSDS indicate adverse skin reactions upon contact. The symptoms of TS were most severe in the upper left arm and on the forehead. The MSDS indicate that the acrylates can cause "skin irritation...redness, swelling, itching..dryness..allergic skin reaction and blistering."

Case Histories

Case #1.

ME is a Swedish female born in 1951. In 1985 she underwent dental repairs which included the use of Dycal in 20 teeth. ME is allergic to sulfonamides, with IGE values reaching 5000. Every dental treatment was followed by aggressive skin reactions of allergic and toxicological nature(Fig.3). All tests for parasites were negative. Her symptoms fulminated into full blown typical sulfa toxicity reactions including oozing skin sores, which also appeared on the nasal septum with bloody scabs and smelly discharge associated with a superimposed infection with Staphylococcus aureus (Fig.7). Other symptoms included loss of memory, kidney pain and urgency, sensitivity to light and electricity fields, pin-prick and moving sensations under the skin, and swelling. After each treatment, ME had problems breathing and talking, and was totally exhausted. She subsequently developed intestinal problems and the skin sores flared up with unbearable itching against which no antipruritic agent helped. Photosensitive reactions presented as the skin became blotchy (Fig.7) with severe burning sensations in the face, throat and chest and a total loss of quality of life.

Dycal was removed in 1991-1992 and initially replaced with Harvard cement. The symptoms were exacerbated with every single removal. ME was confined to bed with strong pains in the face and neck, and in her whole musculo-skeletal system, bowel disturbances and signs of polyneuropathy. A few weeks after the last of the Dycal was removed in February, 1992, most of her sores and rashes disappeared and she could tolerate sunlight (Fig.8). The Swedish clinical practitioners working with ME concluded that Dycal was the underlying cause of her "toxic ulcerative dermatitis."

Case # 2.

Born in Chicago in 1965, JM was a healthy active Caucasian woman until she started experiencing her first symptoms in 1991. By that time, she already had dental work, including 17 fillings. No sealers were used in one filling; Dycal was used in the other 16 fillings. Her earliest symptoms appeared as skin break outs on the face and neck, which was recurrent over the following 9 years. She was treated with minicycline, tetracycline, and acutane along with topical pharmaceuticals. The early episodes were accompanied by body tremors, sleeplessness and joint pain with occasional vomiting of black bile. Thrush appeared in the mouth and around the lips. Pain at the teeth roots persisted throughout the nineties associated

with rapid major decay. A sensation of prickling pain with a pressure and movement under the skin was accompanied by urticaria and skin ulcerations in the same areas that would last for weeks or months. JM's body showed random swelling with red marks in readily observable serpentine-like shapes. The swellings eventually bottle-necked at the knees and ankles. The chest burned and hurt as strange fits of coughing from the lungs ensued. JM then started losing hair as she experienced night fevers and sweats, and peeling of the skin.

During the early 1990's JM was heavily medicated, e.g., Diflucan, Rocefin, Vermox (she had a *Taenia infection), Praziquantel, Ketokonazol, Metrobendazole, among other medications. She experienced some anti-inflammatory relief and occasional temporary clearing of ulcers after which ulcers returned and lasted longer.*

In 1998, massive ulcers appeared on JM's face at the nasiolobial area and at the skin (Fig.9). One ulcer did not resolve for years as it grew deeper while the others cleared within one year. A CBC in 1999 was unremarkable except for a high level of Alpha 1-Globulin of 0.5 (normal range 0.2-0.4) and low levels of IgA of 99 (normal range 60-400) and IgG of 724 (normal range 700-1500). The right ocular cavity was severely painful and JM was beginning to lose her eyesight. JM was then put on a program of Rocefin, Nizoral, Diflucan, Albendazole, Cefelexen, Praziquantel, and a variety of other anti-parasitics. In late 1999, JM started a frequency generation program using a Las Vegas "Genesis" machine while undergoing internal cleansing. This program, along with occasional ozone encephallation helped resolve JM's symptoms to some degree. However, many of the symptoms returned for which a program of Mexican herbs, e.g. Tee Tree, Yerba de Manzo, Yerba de Arnica, as well as MSM liquid, colloidal silver, Male fern extract, Ketokonazol creme, Lamasil creme and tablets, and Ceffalexin was followed.

A major dental repair was completed in 2001 when Dycal was removed from all 16 teeth. After being opened, the teeth were packed with a clove/zinc combination before using zinc oxide and eugenol. Initially, JM experienced a few episodes of sickness, sweats, and vomiting. Since the second visit she was feeling better. After the fourth visit, her eyebrow area had a dramatic reduction in swelling and in the sensation of movement and the red hot congestion of her face and skin resolved. JM's teeth were subsequently rebuilt with gold onlays section by section. By the end of the total repair, Nov.2001, JM regained her normal skin (Fig.10) with no movement sensations or pain anywhere in her body. This state of total resolution has lasted for over one year to the time of this writing without regressions or relapses.

Case #3.

LG, a medium- built white American born in 1957, was in perfect health until the morning of September 18, 1998 when she had a filling in her tooth no. 18 using Dycal as a liner. She experienced severe headache within 2 hours and had to leave work. By 6:00 pm that same evening, she was vomiting and delirious with the headache persisting. She was admitted to the emergency room where her blood pressure was monitored at 169/108 and remained high for the following three years despite repeated attempts to control it with Atenenol and Diazide. LG never experienced high blood pressure or headaches before. An MRI scan was negative. In 1999 LG's health deteriorated progressively. She experienced arthritis- like symptoms in her back, heart palpitations, mitral valve prolapse, fatigue, abnormal pap-smears including pre-cancerous cell abnormalities, night sweats, missed periods, and severe depression. Her Atenenol prescription was increased and various antibiotics were routinely used. By March, 2001, LG, who normally weighed 120 lbs had lost 20 lbs. She was immediately placed on an IV of antibiotics also to combat an abcess near her brain.

In April, 2001, LG moved to an apartment which was heavily infested with mold and mites. Lesions started appearing on LG's face which quickly became red hot as if on fire. Her legs became swollen and painfully burning. By May, 2001, LG had several open lesions (6 mm to 2 cm in diameter) accompanied by erythema, on her face and scalp. Her cheek pulsated as the facial lesions seemed to track to the chin(Fig.11) where the most fulminating lesion was; nearest to her teeth. Springtails (Collembola) and fibers were recovered from these sites. At that time, a CBC analysis showed low lymphocytes of 15.0% (normal 20-43%) and high granulocytes of 77.1% (normal 51-74%), and high rheumatoid factor of 22.6 (normal <20IU/ml). She also tested negative for all communicable diseases at the same time. Her weight dropped to 92 lbs. She started then experiencing movement sensations under the skin of her arms, face and scalp. Lesions started to change shape and acquire track marks around them. Grayish pustular secretions oozed and moved down from the bloody lesions on the scalp and face. The lesion then extended to her legs. At this time LG was diagnosed with stress, anxiety, self-inflicting wounds, acute endocarditis and scabies. Treatments for these conditions did not resolve the NCS symptoms.

OMA diagnosed LG with NCS in January, 2002. She was allergic to sulfa and sulfonamide compounds. Following our protocol, LG had the filling and the Dycal liner removed from tooth #18 in April, 2002. These were replaced with Starflow and Aria (a combination of Bisgma, Tegdma, Lidma and catalysts). Our recommended vitamin supplementation program was then initiated.

By May, 2002, all symptoms were resolved. Once the chin lesion healed, which took a longer time than the rest, the skin of all previously compromised sites returned to normal(Fig.12). Constitutional and neurological functions as well as psychological, emotional and energy levels have also been restored to normalcy.

Conclusion

The toxicity of Dycal, Life and Sealapex has been well documented invivo and invitro studies of various animal and human models by many workers. The toxicity assumed cytotoxic, genotoxic, neurotoxic, phototoxic, necrotic, and inflammatory reactions compatible with the pathology and symptoms observed in NCS patients. Ethyltoluene sulfonamide, common to all three sealants, is considered the primary cause of the NCS. The toluene component, a known nerve toxin, is believed to be responsible, at least in part, for the neurological symptoms. Neurological hyperactivity is related to nerve damage associated with vasomotor reactions due to a direct influence on the peripheral nerve endings.[35]The sulfonamide component is the cause of the cutaneous symptoms, especially in sulfa-sensitive patients and has been demonstrated in elevated sulfonamide/sulfa levels in CBC blood analyses as well as in skin sensitivity tests. The relationship between sulfonamide and phototoxicity has been well established.[29] Resolving the symptoms (effect) by removing the sealants (cause) in patients undergoing treatments, confirms this cause-effect relationship. The toxic effects of other ingredients of these three sealants, e.g., zinc oxide, can not be overlooked.

The nature of causation of NCS precludes contagious transmission. Any similarities of symptoms among partners within the same household are traceable to the transmission of opportunistic infections, especially fungi.

The proper diagnosis of NCS can only be made upon the examination of patients, confirmation of their neurological and dermal symptoms, and the study of their clinical history and medical records, especially dental charts. Additional diagnostic aides include skin tests for allergy to sulfa and blood

analysis for elevated levels of sulfa. Upon the satisfactory diagnosis of an NCS case, and the determination of which teeth have the toxic sealants, arrangements for dental rehabilitation are made. Those include the removal of fillings and of all traces of sealants and replacing them with bio-compatible dental products not containing ethyltoluene sulfonamide or zinc oxide.

It is recommended not to do more than two or three teeth per month. The patient is given a list of vitamins and other supplements to take during the procedure and for the following few weeks until symptoms are completely resolved. The list includes vitamins B12, B6, B5, E, C and folic acid, zinc, calcium, magnesium, omega 3 fish oil or linseed oil, amino acids, *Acidofilus, Bifidus, Lactobacillus,* digestive enzymes and selenium. After reaching the state of normalcy, the patient may still retain some sensitivity to moldy places lacking sun and fresh air circulation. The sealants reported above are still in common usage throughout the world. The "small" amounts continually leaching into the live tissues of the body promote a cumulative progressive damaging pathology over a long period of time. Dental practitioners should be aware of the adverse effects of these products and employ this knowledge to safeguard the well being of their clients.

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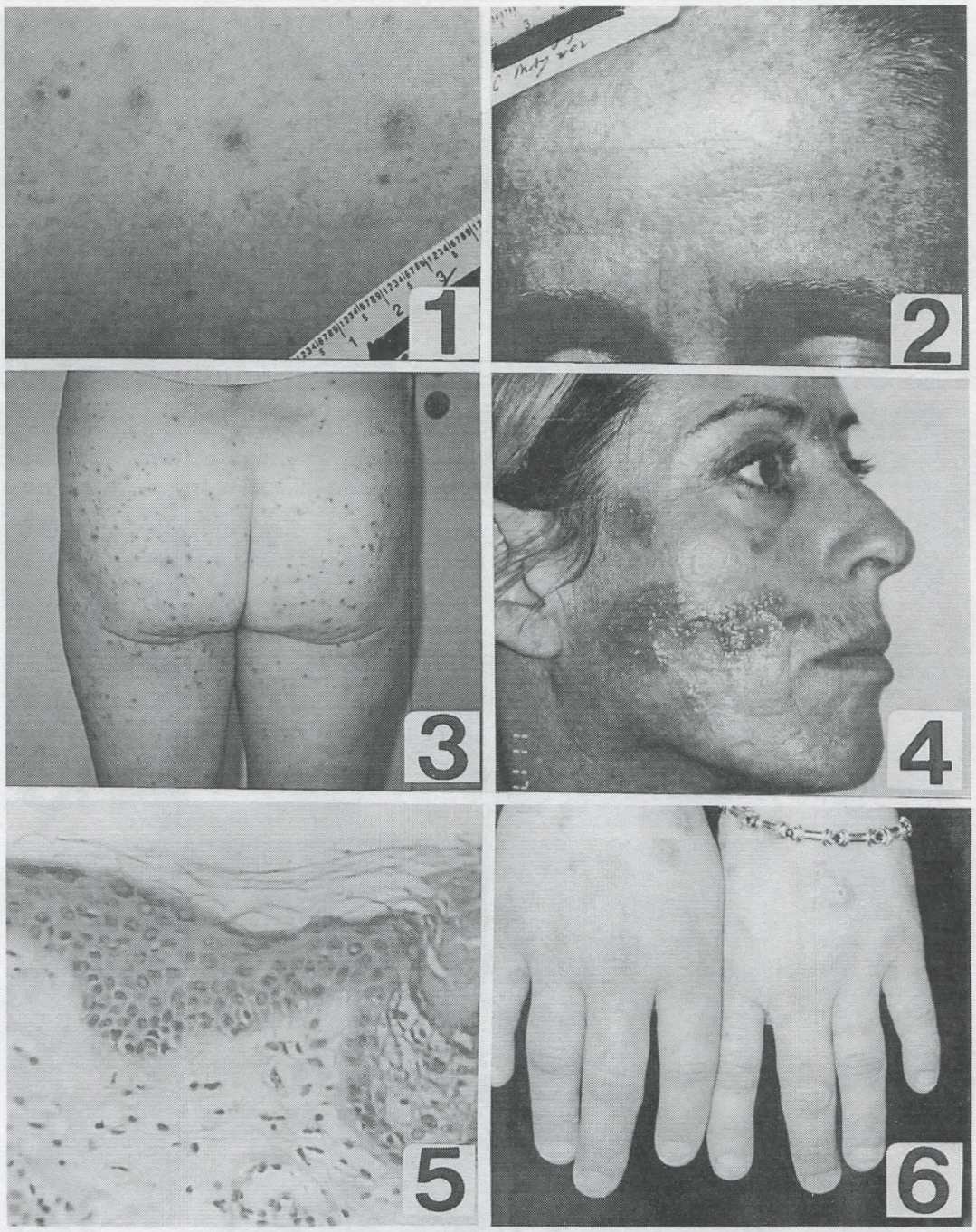
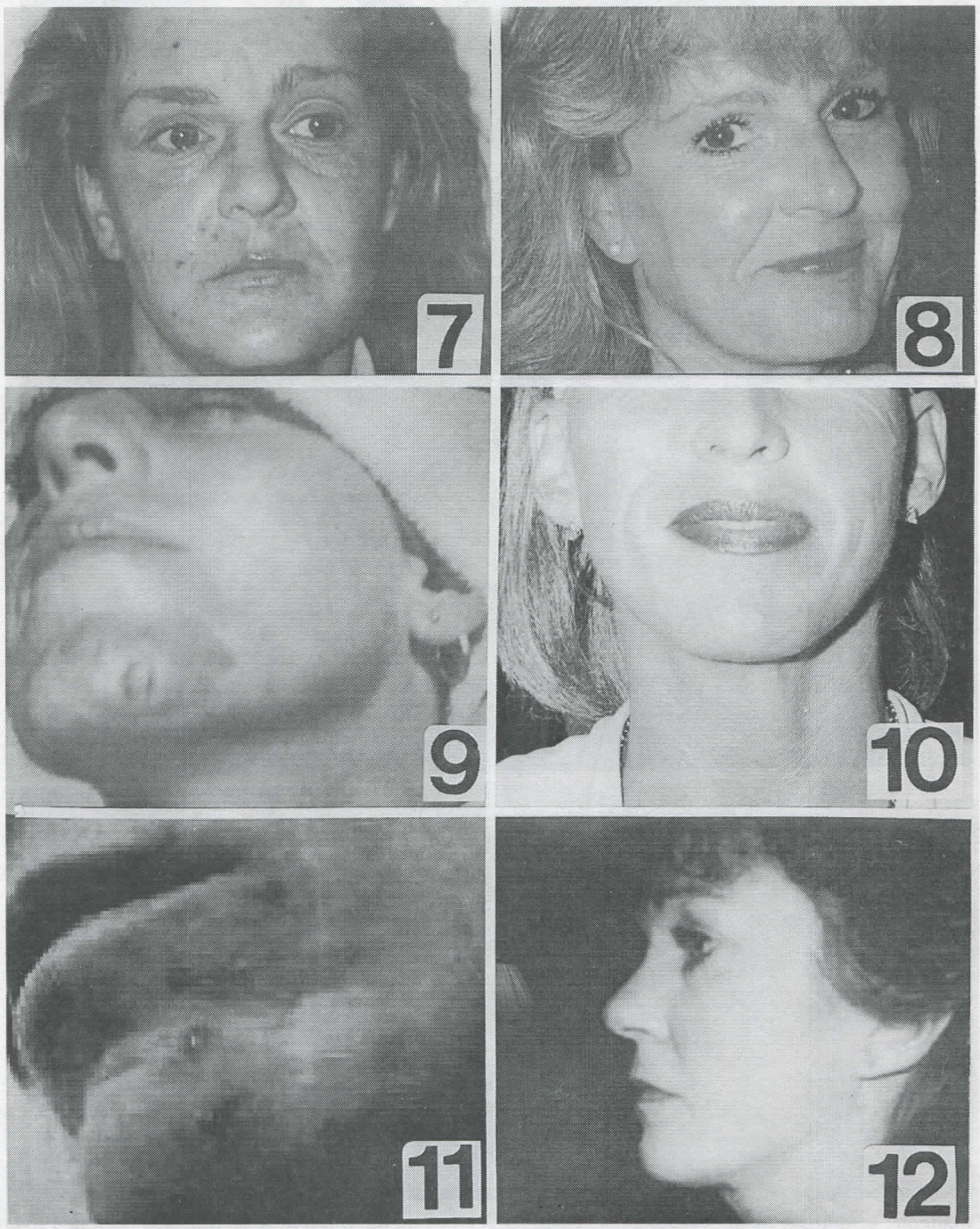


Figs. 1-6. Cutaneous symptoms in NCS patients. 1. Early NCS sores on the thigh of KM. She was born in 1964, compromised with Dycal in two teeth in 1982 and in one tooth in 2002. Neurological symptoms in upper quadrant started in 1997. Cutaneous symptoms began in Spring 2002 preceded by extensive treatment with topical sulfa preparations for possible "mite infestation." Dycal was removed in December, 2002 and recovery is in progress. 2. Elevated sores on the forehead of KM (Fig.1); note the hot red color of the skin. 3. Diffuse NCS sores covering the whole body of ME given Dycal in 1985 (case no.1). 4. Mucoid NCS/lesions on the face of MM. She was born in 1950, given Fynal in six teeth in 1981 and in one tooth in 1986 as well as with Life in two teeth in 1985 and 1988. 5. Histopathological section of one of the roughly 300 sores covering the body of SK. She was born in 1956 and reacted with typical NCS symptoms to a zinc oxide cement (combined with Durelon) underneath a total veneer job in 1982. The section shows hyperkeratosis –like perivascular dermatitis with eosinophils. 6. Cutaneous sores and swelling in the right hand and arm of DB. Born in 1965, DB had 10 amalgam restorations in 1982 and 1983 using Life. She started experiencing symptoms including ulcerated rash all over the body, unilateral edema and pin-prick and subcutaneous movement sensations in 2001-2002. Life is being removed and recovery is in progress.



Figs. 7-12. Facial appearance of the three presented cases before and after recovery from NCS. 7,8 (ME; case no.1); note the hot red face (Fig.7). 9,10 (JM; case no.2); note the lesion on the right cheek and the hot red face (Fig.9). 11,12 (LG; case no.3); note the return of the natural "baby" skin back (Fig.12) after the healing of all facial lesions (Fig.11).

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Table 1- Components in catalysts (C) and bases (B) of Dycal, Life and Sealapex.

Material	Dycal*	Life*	Sealapex
Calcium hydroxide	51% (C)	51% (B)	NG (B)**
Zinc oxide	9.23% (C)	13.75% (B)	NG (B)
Zinc stearate	0.29% (C)	0.25% (B)	_____
Ethyltoluene sulfonamide	39.48% (C)	34% (B)	NG (B)
Silicon dioxide	_____	_____	NG (B)
Titanium dioxide pigment	_____	10.0% (C)	NG (C)
Pigment	0.1% (B)	0.1% (C)	_____
Calcium phosphate	31.0% (B)	_____	_____
Barium sulphate	_____	37.90% (C)	NG (C)
Zinc oxide	9.0% (B)	_____	_____
Methyl silicate	_____	12.0% (C)	_____
Silicon dioxide	_____	_____	NG (C)
Calcium tungstate	17.0% (B)	_____	_____
Butylene glycol disalicylate	43% (B)	_____	_____
Polymethylene mythyl salicylate	_____	38.0% (C)	_____
Isobutyl salicylate	_____	_____	NG (C)

* See Draheim and Murrey.9

** NG = Percentages not given in the manufacturer's (Kerr Corp.) Material Safety Data Sheet published July 28, 2000.