Clinics in Dermatology (2019) **37**, 136–147

ELSEVIER

Clinics in Dermatology

The life-threatening rash of poisoning

Michael Joseph Lavery, MB, BCh, BAO, MRCP (UK) [a,b,*], **Ronni Wolf, MD** [c]

[a] *Department of Dermatology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK*
[b] *Department of Dermatology, Royal Liverpool & Broadgreen University Hospitals NHS Trust, Liverpool, UK*
[c] *Dermatology Unit, Kaplan Medical Center, Rehovot, Israel, and affiliated with the School of Medicine, Hebrew University and Hadassah Medical Center, Jerusalem, Israel*

Abstract Dermatology is frequently viewed by physician and surgical colleagues as a specialty with few emergencies. Although the majority of dermatology practice is in the office setting, cutaneous emergencies do occur through referrals from primary care and as ward consults. Even though cutaneous signs of poisoning would be an uncommon emergency consultation, it is important for dermatologists to be aware of the clinical presentations so as to be able instigate appropriate time critical treatments.
© 2018 Elsevier Inc. All rights reserved.

Introduction

Although thorough history taking is of the utmost importance, examination findings often yield important differential diagnoses, and this is even more relevant with a focused skin examination. Frequently, a detailed skin examination yields diagnostic clues and confirms the diagnosis in patients with a constellation of varying clinical features. In patients with systemic poisoning, there can be such an array of different clinical manifestations and systemic signs that amalgamating all of these into one unifying diagnosis is often challenging, yet life-saving.

Over recent years poisoning has become the focus of much media attention, with the death of Alexander Litvinenko from polonium-210-induced acute radiation syndrome[1,2]; the morbidity inflicted upon Charlie Rowley, Sergei, and Yulia Skripal; and the subsequent death of Dawn Sturgess from the nerve agent Novichok.[3–5] Novichok is an organophosphate compound that inhibits acetylcholinesterase with subsequent contraction and paralysis of muscles—notably respiratory and cardiac muscle—and eventually death.[3,6]

The media coverage of these events, along with the increasing internet and social media use,[7] will inevitably lead to further patient inquiries as well as expectations of "spot diagnoses."

This article focuses on three major areas of cutaneous poisoning: metallic poisoning (mercury, arsenic), carbon monoxide (CO) poisoning, and dioxin (chloracne) poisoning. In addition, Agent Orange (herbicide) and its cutaneous effects are also discussed.

Mercury poisoning

Mercury has been around for thousands of years. Archeologists in Turkey identified that cinnabar (mercury sulfide), mercury's common red ore, and mercury were mined and produced more than 8000 years ago.[8] Mercury was also discovered in an Egyptian tomb at Kurna in 1500 BCE.[9] Over the

* Corresponding author. Tel.: +44 1517062000.
E-mail address: michael.lavery@rlbuht.nhs.uk (M.J. Lavery).

https://doi.org/10.1016/j.clindermatol.2018.12.007
0738-081X/© 2018 Elsevier Inc. All rights reserved.

Table 1 Mercury and its compounds

Mercury compound	Chemical symbol	Examples of use
Mercuric sulfide	HgS	Mercury common ore (cinnabar) Red paint pigment (vermilion)
Mercuric chloride	$HgCl_2$	Wound disinfectant
Mercurous/mercury chloride	Hg_2Cl_2	Antiseptic Skin lightening (calomel)
Mercury nitrate	$Hg(NO3)_2$	Industry—felt hats, cleaning animal pelts
Mercuric oxide	HgO	Batteries

ensuing years, mercury and its compounds have been used in many fields, including science and construction (Table 1).[10] Mercury can still be purchased in its powdered form for use in artwork.[8,11] Due to mercury's shiny appearance and resemblance to silver, Aristotle coined the phrase "quick silver," and Pliny, in 77 CE, labeled its chemical symbol "hydrargyrum" (Hg), Greek for water silver.[12] Mercury was also used for extracting metals, including vermeil (gold-plated silver), and some of the tableware made through this process is evident today in the Vermeil Room in the White House.[8,13] The term "mad as a hatter" and "Danbury shakes" have their origin from the exposure of workers in the felt hat industry to mercury nitrate and other mercuric compounds. Subsequently, the workers developed neurologic impairment, including tremors, slurred speech, abnormal gait, and hallucinations.[14]

Mercury's use in medicine spans thousands of years and was the first reported treatment for syphilis as documented by the Persian physician Ibn Sina (Avicenna) (980-1037 AD) in the *Canon of Medicine* 1025 CE. Mercury had many other medicinal uses, including as an antihelminthic, antiparasitic, antiseptic, and for treating leprosy and typhus.[12,14] In dermatology, mercury was used for treating pruritus and was also commonplace in beauty soaps and skin-lightening creams, due to its melanotoxin properties. A study in the late 1990s performed in Saudi Arabia showed 45% of 38 different skin-lightening creams had mercury levels greater than the Food and Drug Administration's (FDA) acceptable amount of 1 part per million (ppm).[15] A more recent study testing 549 skin-lightening products available in different countries showed that 6% had mercury levels of greater than 1000 ppm, and those products bought in the United States revealed that 3.3% of creams had mercury levels greater than 1000 ppm.[16] This has led to further safety alert warnings issued by the American Academy of Dermatology, the World Health Organization, and the FDA.[17–19]

To this day, mercury still remains a water contaminant, through the improper disposal of paints, lights, and batteries and from the burning of coal from power plants.[20] Once mercury enters the water, there is a continual cycle with sea-life contamination, subsequent mercury accumulation in humans through seafood consumption, and secretion of mercury, which may re-enter the sea or river. Figure 1 highlights the chemical process of obtaining mercury from its common ore cinnabar.[21]

Clinical features

Mercury has three distinct forms—elemental, organic, and inorganic—and the clinical findings will vary depending on the type of mercury exposure.[22] Other pertinent factors determining clinical signs include the source of exposure, exposure duration, medical comorbidities, age of the patient, and differing sensitivity to mercury. Table 2 summarizes the different mercury forms and their clinical effects.[23] Exposure to mercury may also manifest with other cutaneous conditions, including acrodynia, baboon syndrome, cutaneous granuloma, contact dermatitis, or as a mercury exanthem. Table 3 summarizes these clinical features.[23]

When determining which investigative modality to employ, it is important to decipher to which form of mercury the patient was exposed. Although this can be challenging, it will be of clinical relevance when interpreting the results. For example, measurement of urine mercury levels in organic mercury poisoning will be of limited use, as organic mercury is predominately excreted in feces. Urine levels of elemental mercury may display a falsely low or negative result due to poor gastrointestinal absorption. Table 4 summarizes the main investigative methods employed—serum, hair, and urine analysis.[24,25]

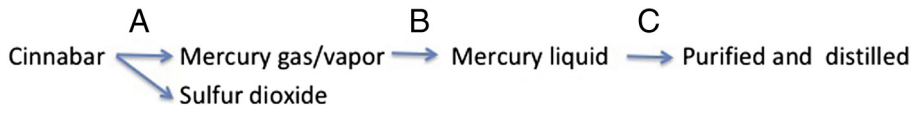

Fig. 1 A, Cinnabar is ground up and heated to 1076°F with the presence of oxygen. Cinnabar contains around 0.011% to 2.98% of divalent mercury. Mercury is released as a gas/vapor along with sulfur dioxide, which is subsequently removed. B, The mercury vapor is cooled, and it becomes liquid mercury. C, Liquid mercury is washed with nitric oxide for purification and then it is distilled.

Table 2 An overview of the different mercury forms

Different forms of mercury	Elemental (metallic)	Organic	Inorganic
Type	Mercury vapor Earth's crust Atmospheric	Methylmercury—converted to elemental mercury in the brain Ethylmercury Thimerosal (49.6% ethylmercury) Alkyl mercury	Mercury vapor—commonest source Divalent mercury salt—most toxic source Converted to elemental mercury in water
Source	Dental amalgams Seafood Thermometers Lamps Mercury-laden latex paint Cutaneous	Seafood (alkyl mercury) Multidose vials influenza vaccines (thimerosal) Plastics, paper Processed wood Insecticides	Skin-whitening products; antiseptic facial creams; bleaching creams Lamps Wood preservatives Pesticides, germicides
Half-life	60 days	45-70 days	42 days
Absorption	Respiratory tract (oxidized to inorganic mercury at alveoli) Limited GI absorption	GI tract (≥95%) Respiratory tract (80%)	Respiratory tract GI tract (2%-10%) Skin (3%-4%)
Pharmacokinetic distribution	99% circulates in: • Blood (plasma protein, glutathione, metallothionein bound) • RBC (Hb bound)	99% circulates in: • Blood (plasma protein, glutathione, metallothionein bound) • RBC (Hb bound)	99% circulates in: • Blood (plasma protein, glutathione, metallothionein bound) • RBC (Hb bound)
Excretion	Predominantly urine Feces	Predominantly feces (90%) Urine (<10%)	Urine and feces Also sweat, breast milk, saliva, tears
Clinical features	Acute • Flu-like prodrome • Pulmonary, GI, Renal, CNS, and GU involvement Chronic • Neuropsychiatric clinical manifestations. Triad: intention tremor, gingivitis, erethism	Neurological (cross BBB as lipid soluble) • Ataxia • Demyelination • Autonomic dysfunction • Mental retardation • Cerebral palsy Renal, liver involvement Birth defects	Gastrointestinal (mercuric salts) • Esophageal erosions • Gingivitis • Burning tongue Renal failure (mercuric salts) Neurological (mercury vapor) • Tremor • Dementia
Cutaneous features	Blue line across gingiva Lichenoid reaction Erythematous papular eruption	Rare or nonexistent	Acrodynia Blue line across gingiva and tongue (marker of systemic poisoning); stomatitis Slate-gray pigmentation (exogenous ochronosis)
Principal organs affected	Kidney Brain Placenta	Brain Kidney Placenta	GI tract Kidney Liver—periportal area
Treatment	Chelation • DMSA (PO) • D-penicillamine (PO)	Chelation • DMPS (IV/PO) • DMSA (PO) • Note: no FDA approval to treat methylmercury or ethylmercury poisoning with chelation therapy	Chelation • DMPS (IV/PO) • DMSA (PO) • D-penicillamine (PO)

BBB, blood-brain barrier; CNS, central nervous system; DMPS, 2,3-dimercaptopropane sulfonate; DMSA, 2,3-dimercaptosuccinic acid; FDA, Food and Drug Administration; GI, gastrointestinal; GU, genito-urinary; Hb, hemoglobin; IV, intravenous; PO, per os (oral); RBC, red blood cell; µg/l, microgram per liter. From Lavery et al.[23] Reproduced with permission from CRC Press.

Treatment

Treatment initiation is often delayed due to delay in diagnosis. The initial step is to remove the patient from the mercury source—moving the patient to a different environment, removing the patients clothing, fomite decontamination, thorough skin cleansing with soap and water, and eye irrigation. Treatment is often reserved for symptomatic patients and those with toxic serum and urine levels. 2,3-Dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMPS) are the two main chelation medicines used; however, the latter does not have FDA approval.[26] Both of these

agents are analogs of dimercaprol, but dimercaprol is rarely used now, due to its adverse neurological profile. Despite DMPS having greater oral bioavailability, DMSA has been shown, in animal studies, to be more effective at chelating methylmercury in the brain.[24] Although there is no set treatment regime, DMPS is generally started at a dose of 5 mg/kg orally, 6 to 8 hourly. DMSA may be administered orally or intravenously at a dose of 10 mg/kg, initially 8 hourly. Alternative chelation therapies include D-penicillamine and chelation combination therapies. It is important to note that there is no FDA approval for any chelation therapy modality for ethylmercury or methylmercury poisoning.[24] Plasma exchange, hemodialysis, and peritoneal dialysis may also be employed.

Table 3 Distinct cutaneous syndromes associated with mercury poisoning

Cutaneous diseases	Features
Acrodynia (pink disease)	dermatologic • Pink, puffy, painful, (pruritic) paresthetic, perspiring, peeling hands • Involvement of the feet, tip of the nose, and cheeks • "Salaam position" (sit with head between the legs while rubbing both hands) • Cold and moist skin • Excoriations, lichenification • Trichotillomania causing alopecia • Erythematous and swollen gingivae from excessive salivation • Oral mucosal ulceration; tooth loss • Nail loss Other • Hypertension, tachycardia • Photophobia • Pelvic girdle and pectoral muscle hypotonia
Acute generalized exanthematous pustulosis (AGEP)	dermatologic • Widespread nonfollicular pustules with underlying edematous erythema Other • Pyrexia • Leucocytosis
Baboon syndrome/SDRIFE (symmetrical drug-related intertriginous and flexural exanthema)	dermatologic • Diffuse, well-demarcated, symmetrical, erythematous maculopapular eruption of the gluteal/perianal area, intertriginous/flexural folds • V-shaped pattern of the inguinal/perigenital area
Mercury exanthema	dermatologic • Diffuse, symmetrical erythema affecting the flexural and proximal extremities. Associated pruritus and burning • Non follicular sterile pustules • Purpura • Desquamation during resolution at around 2 weeks after exposure Other • Fever, malaise • Polydipsia
Contact dermatitis	Acute contact dermatitis • Swelling, vesicles, scaling, irritation Tattoo reaction (red pigment from mercuric sulfide) • Localized swelling and scaling at site of tattoo • Psoriasiform verrucous reaction Dental amalgam reaction • Brown to violaceous papules and plaques; usually adjacent to the dental amalgam
Hyperpigmentation	dermatologic • Slate-gray pigmentation of the treated skin • Mercurialitis—discoloration of the lens from prolonged peri-ocular cream application
Cutaneous granuloma	dermatologic • Flesh-colored to erythematous granulomatous lesion at site of exposure Other • Visceral organ involvement: lungs, kidneys, liver, spleen

From Lavery et al.[23] Reproduced with permission from CRC Press.

Table 4 Investigation modalities for mercury exposure

Investigation	Clinical indication	Result
Blood	Useful for acute exposure	Organic mercury—high blood:plasma ratio up to 20:1 Inorganic mercury: 1:1 to 2:1 ratio
Hair	Useful for chronic exposure especially methylmercury (organic mercury)	Positive if >1 mg/kg
Urine	Useful for exposure to inorganic mercury	Raised VMA and HVA levels

HVA, homovanillic acid; VMA, vanillylmandelic acid.

Arsenic poisoning

Arsenic, from the Greek *arsenikon* meaning potent, is an odorless, tasteless metal that has had a wide array of uses over the years. It had many uses in traditional Chinese medicine, even to this day,[21] and, along with mercury, was used to treat syphilis. It also had cosmetic uses, with the topical application of arsenic, chalk, and vinegar being applied for skin-lightening purposes.[25]

Newspapers in the United States even advertised "arsenic complexion wafers" to remove facial blemishes such as moles and pimples (Figure 2).[27,28] Table 5 highlights common sources for arsenic (and mercury) exposure.

Fig. 2 A, Advertisement for Dr. Campbell's Arsenic Complexion Wafers. Smithsonian. National Museum of American History. B, Advertisement for Dr. Simms' Arsenic Complexion Wafers. *The Salt Lake Tribune,* March 26, 1893: p. 10.

Table 5 Common arsenic and mercury sources of exposure

Arsenic	Mercury
Occupational	Occupational
• Smelting industry	• Mining industry
• Mining industry	• Chemical/electrical engineering
• Semiconductors	• Incineration processes
• Chemical plant	• Agriculture
• Glass manufacturing	Nonoccupational
• Agriculture/factory worker (animal feed, pesticides, fertilizers)	• Seafood—contaminated fish/shellfish
• Painter	• Medicinal (dental amalgams, dermatologic creams/cosmetics)
• Wine maker	• Medical devices—thermometer, sphygmomanometer
Nonoccupational	• Household devices—light bulbs, batteries
• Drinking water (deep water well)	• Horticulture—fungicides, bactericides
• Food	• Electronic devices
• Chinese/Indian/Korean traditional medicine	

From Lavery et al.[23] Reproduced with permission from CRC Press.

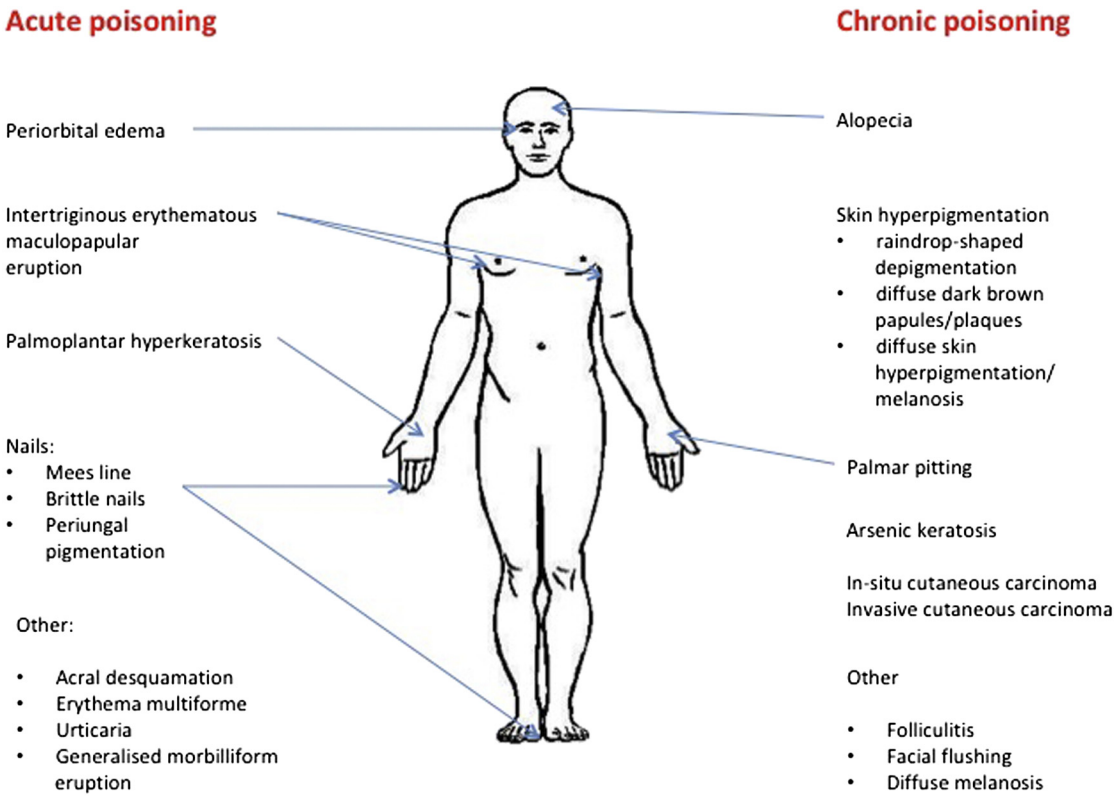

Fig. 3 Acute and chronic cutaneous findings of arsenic poisoning. Adapted and revised from Lavery et al.[23] Reproduced with permission from CRC Press.

Clinical features

The cutaneous features of arsenic poisoning can be divided into acute and chronic, as highlighted in Figure 3. Acute poisoning signs can be subtle and nonspecific and may include periorbital edema, a maculopapular intertriginous eruption, and palmoplantar hyperkeratosis. Nails are often a relevant source of clinical information and this holds true when assessing a patient with arsenic poisoning. Mees lines (Figure 4) depict arsenic deposition at the nail bed[29] and are evident after 2 months of exposure.[30] These transverse bands are 1 to 2 mm wide but are broader in the pediatric population. Patient may also exhibit brittle nails. Although these nail signs are not pathognomonic, it is the constellation of these findings, the presence of other cutaneous signs and clinical features, and the evidence of arsenic exposure through detailed history taking that can be suggestive of arsenic toxicity.

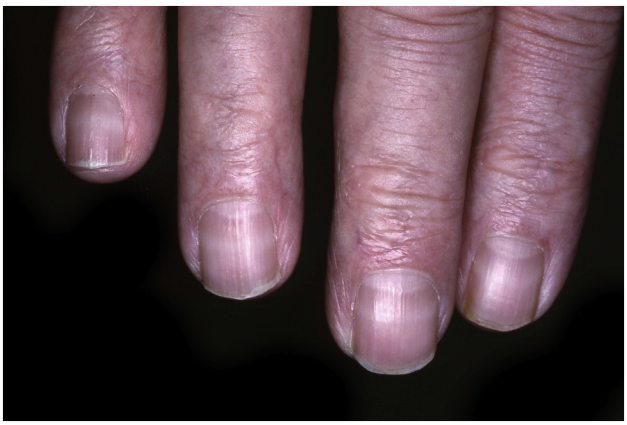

Fig. 4 Mees lines on the fingernails. Courtesy of Louise Barnes, MB, FRCPI; Dublin, Ireland. From Fig. 33.1 of Lavery et al.[23] Reproduced with permission from CRC Press.

Chronic arsenic poisoning has two main features:

- Hyperpigmentation may present as widespread dark brown papules and plaques, raindrop-shaped depigmented macules (also described as raindrops on a dusty road)[31] and papules, or diffuse hyperpigmentation on the upper and lower limbs and trunk (Figure 5). Leukomelanoderma may also be evident.[32]
- The second cutaneous feature in chronic arsenicism is arsenical keratosis (Figure 6), with two variants, simple and nodular. In simple keratosis there is bilateral thickening of acral skin; in nodular keratosis there are nodules on acral sites and/or the feet.[30] There is an increased lifetime risk of malignancies, notably lung and bladder cancer,[33] as well as cutaneous malignancy, both in situ and invasive carcinoma. The invasive cutaneous carcinomas include nonmelanoma skin cancers, as well as Merkel cell carcinoma.[34] Systemic organ dysfunction can also occur, involving the

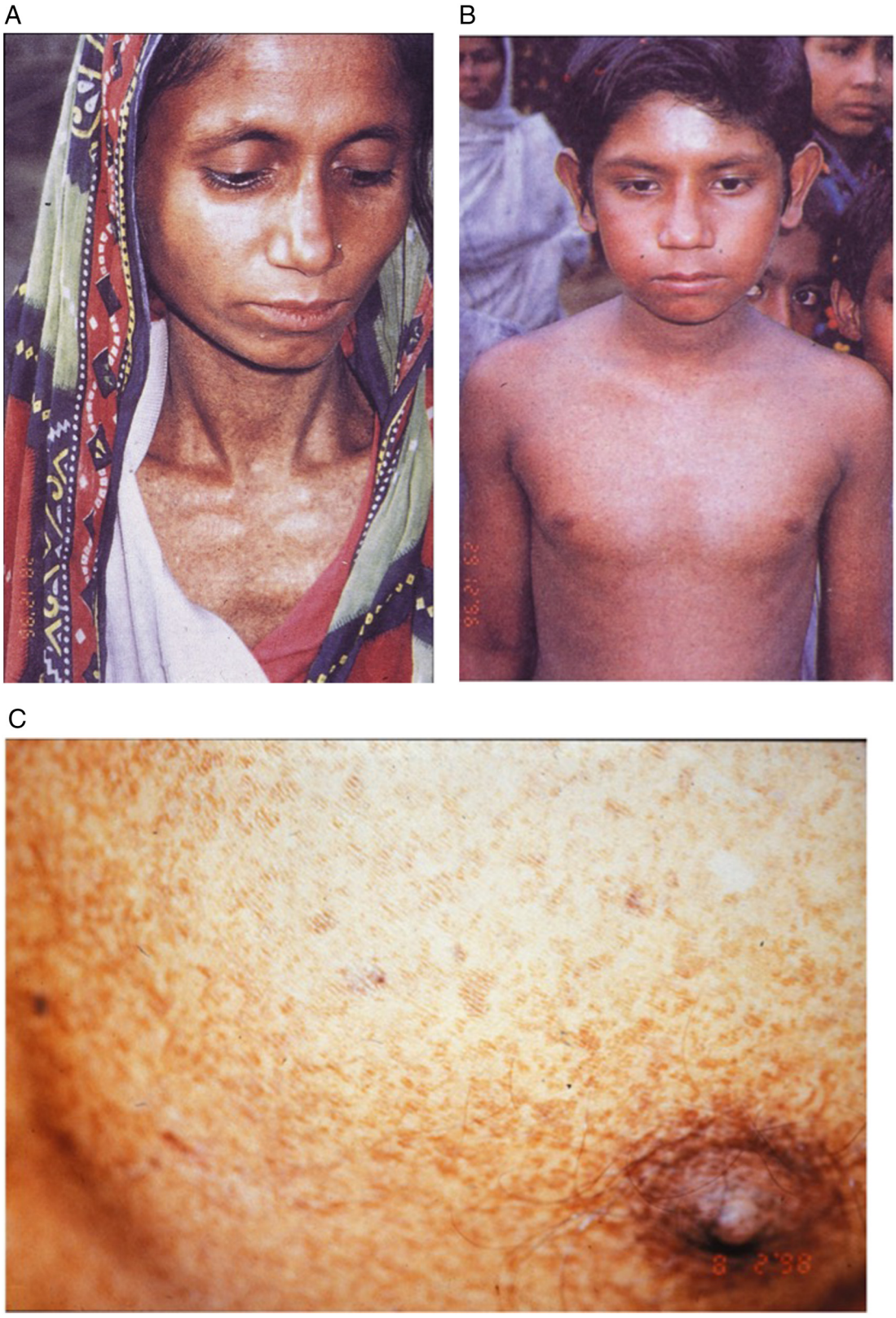

Fig. 5 A, and B, Leucomelanoderma in a woman and a boy exposed to arsenic. C, Leucomelanoderma with raindrop-shaped depigmentation on the left breast. Photographs courtesy of Sue Evans, MD, Liverpool, UK.

gastrointestinal tract, central and peripheral nervous system, and cardiopulmonary, hepatic, and bone marrow involvement. These features are summarized in Table 6.

Management

Once arsenic toxicity is suspected, a serum and urine sample should be sent for immediate analysis. Hair and nail samples are useful in chronic exposure, with pubic hair being preferable and more specific due to less potential contamination, compared with scalp hair.[23] Chelation therapy with DMSA is the mainstay of treatment. Twenty-four-hour urine measurements are subsequently collected for monitoring treatment response. Of note, if signs of carcinogenesis are present, then urine and serum arsenic levels may be too low to measure, and as such chelation treatment may be ineffective.[35] Oral retinoids are often employed as prophylaxis in patients who developed multiple squamous cell carcinomas, especially in the immunosuppressed cohort, and there are reports that oral retinoids may also be of benefit for chemoprophylaxis in patients with arsenic toxicity.[33]

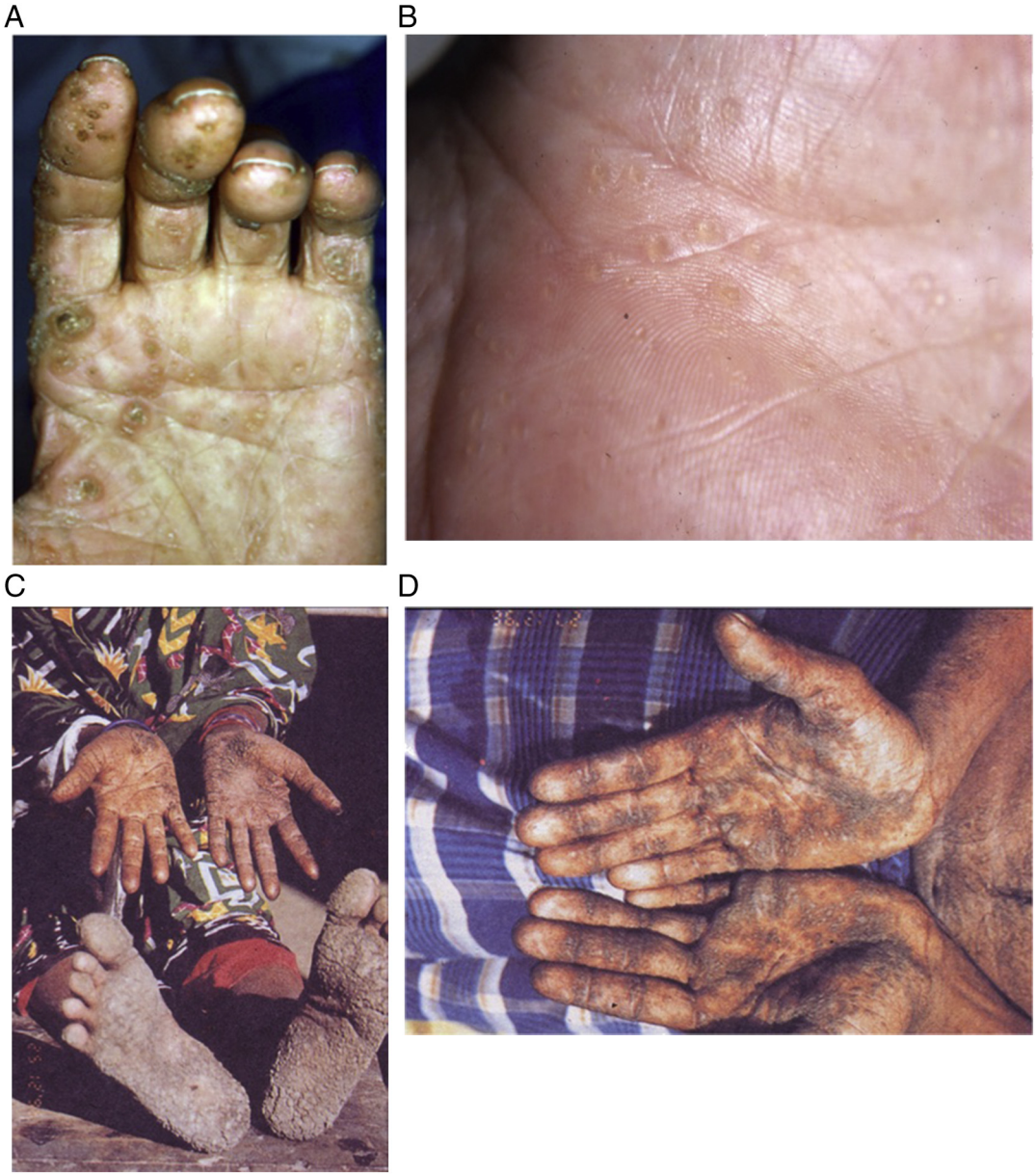

Fig. 6 A, Arsenical keratosis and palmar pitting on the palm of the left hand. This patient had received arsenic in her teenage years for colitis. B, Closer inspection of arsenical keratosis and punctate palmar pitting. C, Gross arsenical palmoplantar keratosis. D, Arsenical keratosis and hyperpigmentation on the palms of both hands. Figure 6A: courtesy of Andrea Franks, FRCP, Chester, UK. Figures 6B-D: courtesy of Sue Evans, MD, Liverpool, UK.

Table 6 Other features of arsenic poisoning

System	Manifestation
Neurological	Symmetrical sensory (axonal, large fiber; glove & stocking distribution) and motor (small muscles hand/feet) neuropathy
	Weakness, headache
	Encephalopathy
	Negative affect on intellectual function
	Cognitive impairment
Gastrointestinal	Colicky abdominal pain
	Nausea and vomiting
	Profuse watery diarrhea ("bloody rice water")
	Excessive salivation
Liver	Hepatomegaly; portal hypertension
Lung	Interstitial pulmonary fibrosis
	Pulmonary edema
Cardiac	Arrhythmias, cardiomyopathy, peripheral vascular disease
Hematological	Bone marrow suppression
	Hemolytic anemia
Malignancy	Skin—in situ carcinoma (AK, Bowens disease); invasive carcinoma (BCC, SCC, Merkel cell)
	Lung
	Genitourinary: renal, bladder
	Gastrointestinal
	Hepatic
Other	Conjunctival congestion; edema of limbs

AK, actinic keratosis; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.
From Lavery et al.[23] Reproduced with permission from CRC Press.

Carbon monoxide poisoning

CO is a colorless, odorless gas, making it so deadly. Once inhaled, it is converted to carboxyhemoglobin. This renders the hemoglobin molecule to retain oxygen, leading to tissue hypoxia and cell death. Patients may be exposed to CO through active and passive cigarette smoke, charcoal grills, fireplaces, and fuel-burning devices. In a number of states it is a regulatory requirement to have CO alarms fitted in homes and workplaces, with Minnesota making CO alarms a requirement in motorboats.[36]

Clinical features can be vague and nonspecific, but become more severe with increasing carboxyhemoglobin levels. Table 7 summarizes these clinical features. Pulse oximetry is not a useful observational modality in patients with CO toxicity as the machine cannot distinguish between carboxyhemoglobin and oxyhemoglobin molecules. An uncoagulated venous sample or an arterial blood sample may be collected for analysis of

Table 7 Clinical features of carbon monoxide poisoning

Clinical manifestations	Signs
Mild (carboxyhemoglobin level <30%)	Cutaneous
• Headache, dizziness, drowsiness, confusion, fatigue, fasciculations	• Cherry red discoloration of skin, mucous membranes
• Palpitations	• Nail: pink discoloration becoming dark blue-red postmortem; Mees lines; erosion and loss of curvilinearity at nailbed border
• Nausea and vomiting	• Generalized erythema, vesicles, bullae
	• Scalp edema, erythema, alopecia
Moderate (carboxyhemoglobin level 30%-40%)	Systemic
• Shortness of breath	• Tachycardia
• Chest pain	• Tachypnea
	• Hypotension
	• Cardiac arrhythmias
	• Seizures, coma
Severe (carboxyhemoglobin level >40%)	
• Palpitations	
• Confusion	
• Paralysis	

the CO level. Treatment involves either high flow oxygen for up to 6 hours, with carboxyhemoglobin levels decreasing in 80 minutes[37]; or hyperbaric oxygen with carboxyhemoglobin levels decreasing in 22 minutes.[38]

Dioxin poisoning

Dioxins are a group of lipophilic polyhalogenated, polychlorinated aromatic hydrocarbons,[39] with 2,3,7,8-tetrachlorodibenzoparadioxin (TCDD) being the most toxic chemical in this family.[23] Dioxins are generated as byproducts in chemical reactions, which use chlorine. Herbicides are produced through chemical reactions,[40] and as TCDD may also be formed as a byproduct, dioxins can be found in soil and water and may be inadvertently consumed, either directly or through consumption of meat and fish. Dioxins may also be used as a poison, with Viktor Yushchenko, poisoned in 2004 at a dinner party in London, being the most infamous case (Figure 7).[40] Dioxin was also inadvertently released from the ICMESA chemical plant in Meda, Italy, in 1976, leading to a large-scale industrial exposure, and subsequent development of both cutaneous and internal signs of dioxin toxicity.[41,42]

During the Vietnam War, Agent Orange was commonly employed to destroy enemy crops. Agent Orange is a concoction of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenpxyacetic acid (2,4,5-T). 2,4,5-T is produced through a chemical process, with TCDD produced as a byproduct; Agent Orange, therefore, unwittingly became contaminated with dioxin and led to mass exposure among American veterans.

Exposure was mainly through handling of Agent Orange, rather than through incidental exposure to ground troops. This was due to the rapid photochemical degradation and limited bioavailability of TCDD, as well as accurate delivery of TCDD to the crop fields by the airplanes.[43]

Chloracne is pathognomonic for dioxin exposure, and there is a strong association between plasma levels of TCDD and chloracne.[44] Dioxin is excreted from sebaceous glands, and therefore chloracne is predominantly characterized by comedonal lesions, mainly closed comedomes, although inflammatory lesions such as nodules and cysts may also occur. The face is the most common site afflicted; however, chloracne may also be seen at postauricular, axillary, and inguinal sites, with the trunk and genitalia rarely being involved.[23] Chloracne may be difficult to distinguish from other variants of acne, but the predominance of comedonal lesions and the involvement of virtually every vellus hair follicle histologically can aid in differentiation. Histopathology may also reveal multiple infundibular cysts with central collections of eosinophilic granular or laminated sebum.[45] These histopathology findings are witnessed in small numbers of patients who had biopsies. Other cutaneous manifestations include porphyria cutanea tarda, diffuse hyperpigmentation, soft-tissue sarcomas (eg, leiomyosarcoma and dermatofibrosarcoma protuberans), and cutaneous lymphoma.[39] The U.S. Department of Veterans Affairs has recognized chloracne and porphyria cutanea tarda as conditions with presumptive connections to exposure to Agent Orange.[46]

The liver is the most common internal organ involved, with other clinical features such as diarrhea, polyneuropathy, headache, conjunctivitis, thrombocytopenia, and hypertriglyceridemia.[47] Clinical manifestations may occur many months to years after the original exposure, and may be due to the long half-life of dioxin (5-10 years with TCDD)[48] as well as the storage of dioxin in fatty tissue with subsequent slow elimination. Persistently high levels of plasma TCDD in patients exposed to dioxin after the Seveso disaster, 20 years prior, highlight this.[44]

Treatment can be challenging. Due to the predominance of comedonal lesions, both topical and oral retinoids have been employed with some improvement. Medication to hasten the elimination and excretion of TCDD has been trialed, with

Fig. 7 Photographs of Victor Yushchenko before poisoning A, and 3 months B, and 3.5 years C, after poisoning with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Image from Sorg et al.[48] Reproduced with permission from Elsevier.

Olestra, a lipophilic dietary fat substitute, showing a reduction in dioxin half-life from 7 years to 1 to 2 years.[49]

Conclusions

Cutaneous signs of poisoning are not regularly encountered by dermatologists in the office, but recent media coverage highlighting exposure to different toxins has brought this topic to the fore. It is imperative to take a detailed history from the patient, close relative, or friend; perform a thorough detailed physical examination; remove any source of contamination; perform relevant investigations; and instigate appropriate treatment, both to the patient and to those exposed, to improve patient outcome.

References

1. Nathwani AC, Down JF, Goldstone J, et al. Polonium-210 poisoning: a first hand account. *Lancet* 2016;388:1075-1080.
2. Harrison J, Fell T, Leggett R. The polonium-210 poisoning of Mr Alexander Litvinenko. *J Radiol Prot* 2017;37:266-278.
3. Patocka J. Novichok agents—mysterious poisonous substances from the cold war period in press. *Mil Med Sci Lett* 2018;87:1-3.
4. BBC News. Russian spy: what happened to sergei and yulia skripal? BBC News website. https://www.bbc.co.uk/news/uk-43643025 Updated 2018. Accessed September 2018.
5. Amesbury poisoning: Experts confirm SubStance was novichok. BBC News website. https://www.bbc.co.uk/news/uk-45411557 Updated 2018. Accessed September 2018.
6. Hosseini SE, Saeidian H, Amozadeh A. Fragmentation pathways and structural characterization of organophosphorus compounds related to the chemical weapons convention by electron ionization and electrospray ionization tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2016;30:2585-2593.
7. Basch CH, Brown AA, Fullwood MD. YouTube as a source of information on skin bleaching: a content analysis. *Clin Exp Dermatol* 2018;43:399-403.
8. Brooks W. Industrial use of mercury in the ancient world. In: Bank M, ed. Mercury in the Environment: Pattern and Process. 1st ed. Berkeley, CA: University of California Press; 2012. p. 19-24.
9. Graeme KA, Pollack Jr CV. Heavy metal toxicity, part 1: arsenic and mercury. *J Emerg Med* 1998;16:45-56.
10. Blaszczak-Boxe A. Facts about mercury (Hg). https://www.livescience.com/39232-facts-about-mercury.html Updated 2014. Accessed August 2018.
11. Iconfile Resource guide. http://www.iconofile.com/default.asp?dir=guide&page=showresource&SupplierID=30. Accessed August 2018.
12. Ozuah P. Mercury poisoning. *Curr Probl Pediatr* 2000;30:91-99.
13. Vermeil room. http://www.whitehousemuseum.org/floor0/vermeil-room.htm. Accessed August 2018.
14. Sunderman F. Perils of mercury. *Ann Clin Lab Med* 1988;18:89-101.
15. Al-Saleh I, Al-Doush I. Mercury content in skin lightening creams and potential hazards to the health of saudi women. *J Toxicol Environ Health* 1997;51:123-130.
16. Hamann C, Boonchai W, Wen L. Spectrometric analysis of mercury content in 549 skin-lightening products: is mercury toxicity a hidden global health hazard? *JAAD* 2014;70:281-287.
17. American Academy of Dermatology. Skin lightener containing mercury can cause serious health problems. https://www.aad.org/public/skin-hair-nails/skin-care/skin-lighteners. Accessed August 2018.
18. World Health Organisation. Mercury in skin lightening products. http://www.who.int/ipcs/assessment/public_health/mercury_flyer.pdf Updated 2011. Accessed August 2018.
19. U.S. Food and Drug Administration. Mercury products linked to skin products. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm294849.htm Updated 2016. Accessed August 2018.
20. Dantzig PI. A new cutaneous sign of mercury poisoning. *J Am Acad Dermatol* 2003;49:1109-1111.
21. Yu W, Zhang N, Qi J. Arsenic and mercury containing traditional chinese medicine (realgar and cinnabar) strongly inhibit organic anion transporters, oat1 and oat3, in vivo in mice. *Biomed Res Int* 2015;2015, 863971.
22. Boyd AS, Seger D, Vannucci S. Mercury exposure and cutaneous disease. *J Am Acad Dermatol* 2000;43:81-90.
23. Lavery MJ, Stull C, Wolf R. Cutaneous signs of poisoning. In: Wolf R, Parish LC, Parish J, eds. Emergency Dermatology. 2nd ed. Boca Raton, FL: CRC Press; 2017. p. 314-322.
24. Ye BJ, Kim BG, Jeon MJ. Evaluation of mercury exposure level, clinical diagnosis and treatment for mercury intoxication. *Ann Occup Environ Med* 2016;28:5.
25. Ellenhorn M, Schonwald S, Ordog G. Metals and related compounds. In: Ellenhorn M, ed. Ellenhorn's Medical Toxicology. 2nd ed. Baltimore: Williams and Wilkins; 1997. p. 1532-1613.
26. Zalups RK, Bridges CC. Relationships between the renal handling of DMPS and DMSA and the renal handling of mercury. *Chem Res Toxicol* 2012;25:1825-1838.
27. The Salt Lake Tribune. 1893:10. Available from:https://www.newspapers.com/image/?spot=865175&fcfToken=4f6b7876614a78746162714e4a4d327769665336634e6f5a30436256416444354e356e5153417565 4f7569684b5374673448736f6b6176374f6d664242313546. Accessed August 2018.
28. National Museum of American History. Cosmetics and personal care products in the medicine and science collections. Skin carex. Smithsonianhttps://www.si.edu/spotlight/health-hygiene-and-beauty/skin-care. Accessed August 2018.
29. Dobbs MR. Approach to the outpatient with suspected neurotoxic exposure. Clinical Neurotoxicology. Syndomes, Substances, Environments. 1st ed. Philadelphia: Saunders; 2009. p. 17-29.
30. Davidovich B, Wolf R. Skin signs of poisoning. In: Wolf R, Davidovich B, Parish J, Parish LC, eds. Emergency Dermatology. 1st ed. Cambridge, England: Cambridge University Press; 2011. p. 318-328.
31. Nambi R. Dermatological manifestations of metal poisoning. In: Griffiths CE, Barker J, Bleiker T, Chalmers R, Creamer D, eds. Rook's Textbook of Dermatology. , 9th ed.New York: Wiley-Blackwell; 2016. p. 122.2-122.3.. chapter 122.
32. Sengupta SR, Das NK, Datta PK. Pathogenesis, clinical features and pathology of chronic arsenicosis. *Indian J Dermatol Venereol Leprol* 2008;74:559-570.
33. Wollina U. Arsenic and skin cancer—case report with chemoprevention. *Our Dermatol Online* 2016;7:172-175.
34. Lien HC, Tsai TF, Lee YY. Merkel cell carcinoma and chronic arsenicism. *J Am Acad Dermatol* 1999;41:641-643.
35. Duker AA, Carranza EJ, Hale M. Arsenic geochemistry and health. *Environ Int* 2005;3:631-641.
36. National Conference of States Legislatures. Carbon monoxide detector requirements, laws and regulations. Carbon monoxide detector requirements, laws and regulations website. http://www.ncsl.org/research/environment-and-natural-resources/carbon-monoxide-detectors-state-statutes.aspx Updated 2018. Accessed August 2018.
37. Hatami M, Naftalin F, Khatamee MA. Abnormal fingernail beds following carbon monoxide poisoning: a case report and review of the literature. *J Med Case Rep* 2014;8:263.
38. Hampson NB, Hauff NM. Risk factors for short-term mortality from carbon monoxide poisoning treated with hyperbaric oxygen. *Crit Care Med* 2008;36:2523-2527.
39. Patterson AT, Kaffenberger BH, Keller RA. Skin diseases associated with agent orange and other organochlorine exposures. *J Am Acad Dermatol* 2016;74:143-170.

40. Sterling JB, Hanke CW. Dioxin toxicity and chloracne in the ukraine. *J Drugs Dermatol* 2005;4:148-150.
41. Bertazzi PA, Consonni D, Bachetti S. Health effects of dioxin exposure: a 20-year mortality study. *Am J Epidemiol* 2001;153:1031-1044.
42. Michalek JE, Pirkle JL, Needham LL. Pharmacokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in seveso adults and veterans of operation ranch hand. *J Expo Anal Environ Epidemiol* 2002;12:44-53.
43. Young AL, Giesy JP, Jones PD. Environmental fate and bioavailability of agent orange and its associated dioxin during the vietnam war. *Environ Sci Pollut Res* 2004;11:359-370.
44. Baccarelli A, Pesatori AC, Consonni D. Health status and plasma dioxin levels in chloracne cases 20 years after the seveso, italy accident. *Br J Dermatol* 2005;152:459-465.
45. Pastor MA, Carrasco L, Izquierdo MJ. Chloracne: histopathologic findings in one case. *J Cutan Pathol* 2002;29:193-199.
46. US Department of Veterans Affairs. Agent orange newsletter. skin conditions qualifying for presumptive service connection. https://www.publichealth.va.gov/exposures/publications/agent-orange/agent-orange-summer-2017/skin-conditions.asp Updated 2017. Accessed August 2018.
47. Dunagin WG. Cutaneous signs of systemic toxicity due to dioxins and related chemicals. *J Am Acad Dermatol* 1984;10:688-700.
48. Sorg O, Zennegg M, Schmid M. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) poisoning in viktor yushchenko: identification and management of TCDD metabolites. *Lancet* 2009;374:1179-1185.
49. Geusau A, Tschachler E, Meixner M. Olestra increases fecal excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Lancet* 1999;354:1266-1267.