# Alkalis and Skin

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**The aim of this editorial is to provide an overview of the chemical interactions occurring in the skin of our patients on contact with alkaline agents. Strongly basic alkali is highly aggressive and will readily hydrolyze (or cleave) key biological molecules such as lipids and proteins. This phenomenon is known as saponification in the case of lipids and liquefactive denaturation for peptides and proteins. A short section on current first-aid concepts is included. A better understanding of the basic science behind alkali burns will make us better teachers and provide an insight into the urgency needed in treating these common and dangerous chemical injuries. (J Burn Care Res 2016;37:135–141)**

## ALKALIS

Between July 1, 2009, and June 6, 2014, the Adult Burn Service at the Royal Adelaide Hospital in Adelaide, South Australia, dealt with 1913 admissions, of which 124 (6.5%) were injuries because of chemical exposure. Of these, 80 (4.2% of all admissions and 64.5% of chemical burns) were because of alkalis. There were no deaths as a result of chemical injury. Obviously, the proportion of chemical burns admitted by an individual unit will reflect the hazards within the catchment area. Published figures for chemical injury range between 3.2 and 18.7% of the total burn number,[1–7] and the mortality rate for chemical injuries ranges from 0.7 to 30%.[4,7,8]

The word Alkali derives from Arabic (Al Qaly), which literally translates as "calined ashes" since the ash left after burning certain plant stems (eg, glasswort), when dissolved in water, formed strong alkaline solutions. Such ash was referred in Old English as "Potash." In chemistry, an alkali is defined as a soluble base and we now know that these alkalis are the hydroxides of alkali metals (lithium, sodium, potassium, rubidium, cesium, francium), alkaline earth metals (beryllium, calcium, magnesium, barium, strontium, radium), and other compounds that produce alkaline hydroxides in solution (such as gaseous ammonia). They are often given the term *caustic*, defined as being able to burn or corrode organic tissue by chemical action. The general structure of an alkali is $M^+ {}^-OH$, where $M^+$ is the alkali metal cation and $^-OH$ the caustic hydroxide anion.

Alkalis (MOH) are strong bases and as a consequence are readily protonated by acids (HA) to produce the conjugate acid of the alkali ($H_2O$) and the salt of the acid ($A^-M^+$), in what is a classic acid/base reaction.

$$M^{+-}OH + HA \rightarrow M^{+-}A + H_20$$

They also readily hydrolyze organic compounds such as esters and amides as commonly found in key biomolecules within the skin and more widely in cells. The basicity of alkalis means that in water they have a pH >7 and as such will turn the acid–base indicator phenolphthalein from clear to pink or red and litmus paper to blue.

Alkalis are common in industrial and household settings. Many household cleaning agents, particularly oven or kitchen cleaners and car-cleaning products (alloy wheel or paint or radiator) are strongly caustic.[9] As oven-cleaning agents, alkalis saponify or hydrolyze "baked-on" food grease and fats, making their removal easier. Their ability to do the same to skin and ocular cornea or conjunctiva is what makes them dangerous. Chemical materials to unblock "blocked" drains are similarly hazardous. In all of these situations, the caustic agent is used to breakdown or hydrolyze grease, fats, and organic materials.

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Kneeling in wet cement or concrete during "screeding" causes many burn injuries every year. In these cases, calcium oxide ("lime," a constituent of cement and concrete), dissolves in the water used when mixing, to form calcium hydroxide. This agent is less aggressive than alkaline metal hydroxides and the progressive burn is often painless, but deep. Burn surgeons concentrate mostly on the effect of alkalis on protein, where degradation by liquefaction (colliquative or liquefactive necrosis), but considerable lipid destruction occurs before structural protein is exposed.

## PATHOPHYSIOLOGY

The severity of burn injury caused by alkali depends on its basicity, concentration, volume, and state (solid vs liquid) which impacts on its ability to "penetrate" and hence the duration of skin contact.

There are three factors involved in the mechanism of injury from strong alkali[9]:

1. Saponification of fat results in the loss of the natural water barrier provided by lipids, hence allowing increased water penetration of the alkali. This exothermic reaction also contributes to thermal injury.
2. The hygroscopic nature of alkalis allows them to dehydrate cells leading to cell death.
3. Alkalis attack proteins, forming water-soluble alkali proteinates, which contain carboxylate ions that cause subsequent and ongoing liquefactive necrosis.

## LIPIDS

Fatty acids are the characteristic building blocks of most lipids.[10] These carboxylic acids contain a long hydrophobic (nonpolar) carbon chain of up to 24 carbon atoms that can be saturated (ie, no carbon–carbon double bonds) or unsaturated with one or more carbon–carbon double bond. Fatty acids form simple waxy esters, but more generally they combine with other chemical structures to produce the different classes of lipid. Triglycerides (fats) are formed on joining three fatty acids to glycerol, each via an ester bond as shown in Figure 1A. Phospholipids, the main component of cellular membranes, have one of the fatty acid chains replaced by a polar head group attached to one of the glycerol oxygens as shown in Figure 2A. There are a number of variants on this theme, including sphingolipids that contain a modified glycerol subunit (such as choline) and also esters of cholesterol. The nonpolar carbon chains of all these

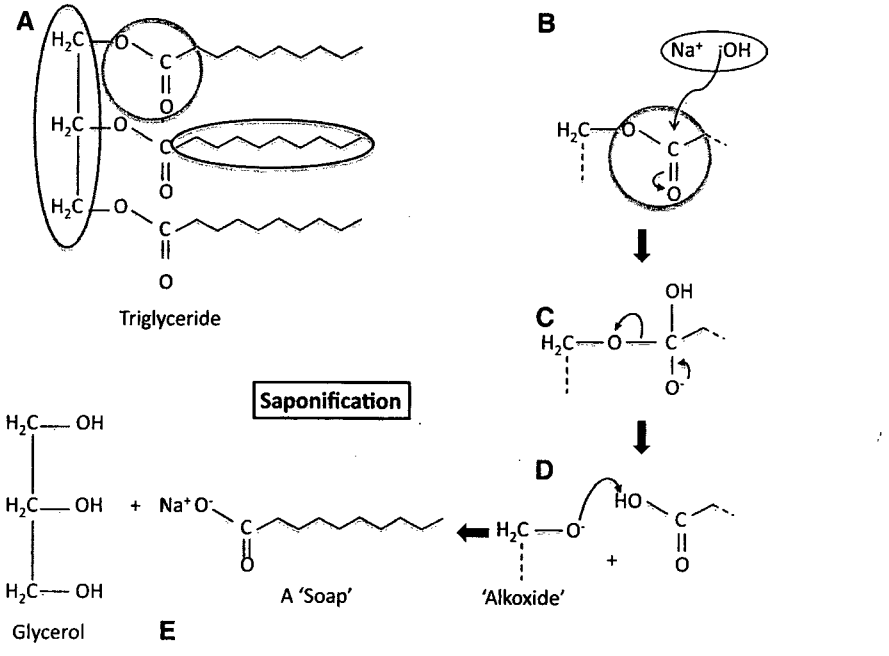


**Figure 1.** Saponification. A. The ester linkage is the site vulnerable to attack by the alkali hydroxide. B. The hydroxide attacks the carbonyl carbon. C. Once attached, its presence weakens the ester bond to the glycerol spine which breaks leaving a carboxylic acid group on the fat and an "alkoxide" on the glycerol spine (D). The alkoxide is more basic than the OH of the carboxylic acid and it abstracts the proton to give the sodium carboxylate salt or "soap" and glycerol (after similar cleavage of all three triglyceride ester bonds). This process of soap formation is called saponification.

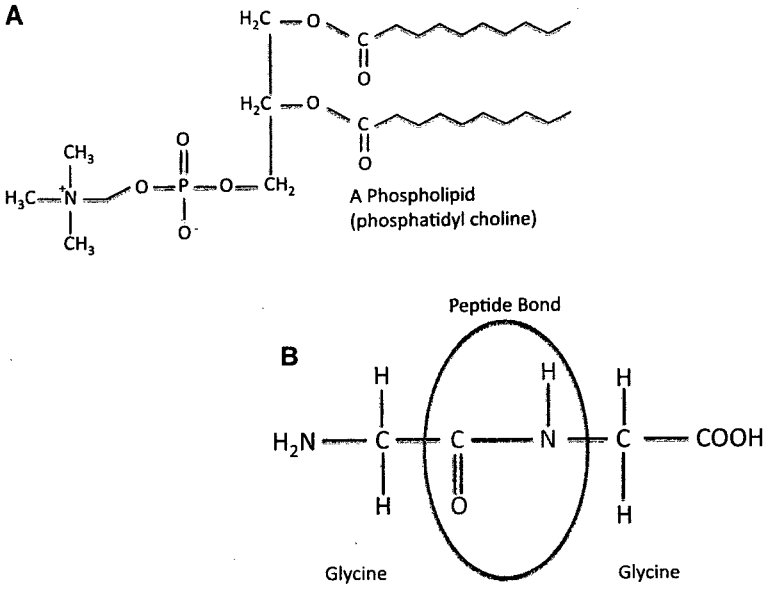


**Figure 2.** Phospholipid structure and peptide bond denaturation. A. Phospholipids have a similar structure to triglycerides, with one of the fatty acid chains replaced by a polar phosphate group. Additional groups are attached to the phosphate to give more complex lipids. B. The peptide bonds that link all the amino acids in protein are attacked in the same way that the hydroxide anion attacks the amide bond in ceramide. The destruction of the three-dimensional protein structure and liberation of the constituent water- and fat-soluble amino acids make the protein "liquefy."

membrane lipids associate to form a bilayer, with the polar head groups exposed to the aqueous environment. All these lipids contain one or more reactive ester linkages that can be hydrolyzed by a process known as saponification as discussed below.

## PROTEINS

Proteins are linear polymers of amino acids linked together by amide or peptide bonds[10] (Figure 2B). These linear sequences fold into a well-defined 3D-conformation (or shape) that defines the function of the protein. This folding occurs at a number of levels; small segments of well-defined conformation referred to as secondary structure (eg, an α-helix or β-pleated sheet), the entire conformation of each chain (tertiary structure), and multi-subunit folding and interactions referred to as quaternary structure. All this folding is dictated by non-covalent interactions, including hydrogen bonding, salt bridges, hydrophobic-hydrophobic interactions, and hydrophilic-hydrophilic interactions. Disruption of this structure (referred to as denaturation) results from chemical hydrolysis with alkalis, or by simply changing the pH or other external parameters. In all cases, this leads to a loss of protein function and in the case of hydrolysis, cleavage into smaller fragments as discussed below.

### Fat Saponification

The term "saponification" is introduced into the dictionary of children embarking on a chemistry syllabus early in their high school education. This process can be illustrated by placing a drop of sodium or potassium hydroxide onto the pulp of the child's index finger, and encouraging them to rub index and thumb pulps together. The "slippery" sensation experienced is hopefully short-lived as the hand is then thrust under running water to dilute the alkali and stop the reaction. The teacher intones that the alkali has converted the fats in the skin into soap, hence the slippery feeling. Although strong acids can also catalyze the process, hydrolysis of fats in the commercial process of soap production is invariably performed by sodium or potassium hydroxide.

The process of saponification refers to the irreversible hydrolysis of the ester groups of natural fats and lipids into glycerol and free fat acids, with the liberation of water[11] illustrated in Figure 1. If this reaction is performed with alkali, then the free carboxylic acids (fatty acids) react further by deprotonation to give the salt of the acid, which is essentially a soap. These soaps can emulsify other nonpolar material, such as other fats and grease, by acting as detergents and encapsulating them in a shell or droplet structure, which has the long carbon chains associated in the nonpolar interior and the polar carboxylate head groups exposed to the aqueous environment.

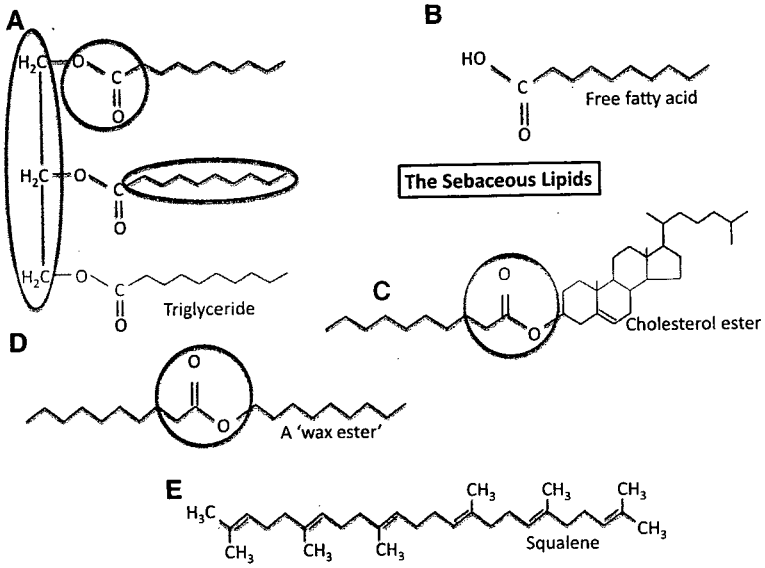


**Figure 3.** The sebaceous lipids. A. Triglycerides make up 45 to 50% of the sebaceous lipids. They consist of a glycerol "spine" (red oval) to which are attached three variable fatty acids (purple oval) via an ester linkage (green oval). B. Free fatty acids form 10% of sebum, variable long aliphatic chains with terminal carboxylic acid residues. C. Cholesterol esters make up less than 5% of the sebaceous lipids but contain the vulnerable ester linkage, the disruption of which releases cholesterol and a free fatty acid. D. Squalenes are stable to alkali attack and comprise 12% of the sebaceous lipids. E. Wax esters are long aliphatic chains linked by an ester that is cleaved by alkali to liberate a fatty acid and a long chain alcohol. They make up 25% of the sebaceous lipids.

## EPIDERMAL SURFACE LIPIDS

Epidermal surface lipids are the first materials to come into contact with a base during an alkali burn. Saponification then leads to destruction of the cellular membrane of skin cells. While the associated chemical hydrolysis reaction is straight forward, little is known about the associated biology. There are two main groups of epidermal surface lipids: sebaceous lipids and epidermal lipids.[12] Lipids of sebaceous

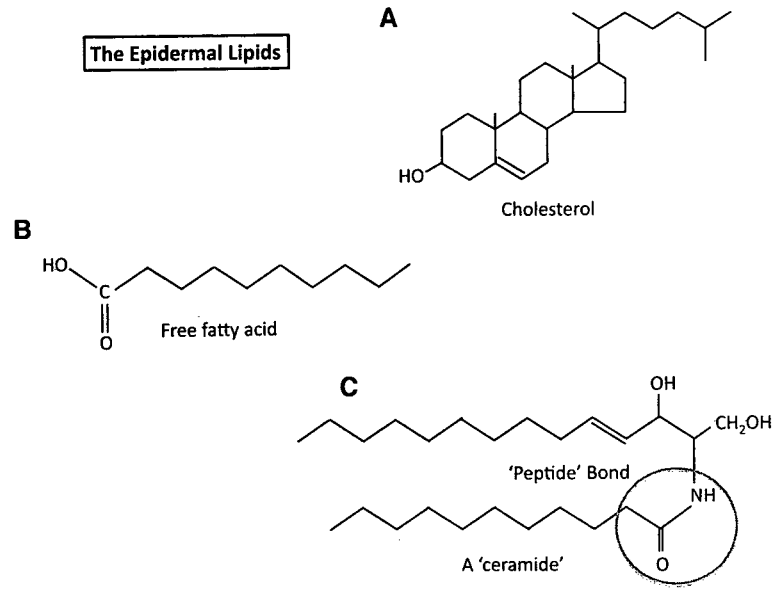


**Figure 4.** The epidermal lipids. A. Cholesterol, which makes up a third of the epidermal lipids, is stable to alkali attack. B. Free fatty acids also make up a third of the epidermal lipids and these compounds are not hydrolyzed further by alkali, rather they are simply deprotonated to give a soap. C. Ceramides contain an "amide bond" (similar to a peptide bond) which, when broken by alkali, liberates a free fatty acid and an aliphatic diolamide (eg, sphingosine).

origin are the products of holocrine secretion from sebaceous glands, closely associated with hair follicles (Figure 3). These products are secreted onto the surface of the skin and are primarily non-polar lipids such as triglycerides, wax esters, and squalenes. Epidermal lipids, in contrast, fill the spaces between the cells and are composed of a mixture of ceramides, free fatty acids, and cholesterol[13] (Figure 4).

Since greater than 70% of sebaceous lipids are esters, triglycerides, and wax esters, the alkaline hydrolysis disrupts this first line of waterproofing mechanical barrier. As the sebaceous lipids are destroyed, the surrounding environment becomes more polar, allowing the hydroxide anions to penetrate into the stratum corneum and the epidermal lipids. Eleven subclasses of ceramide have been identified in human stratum corneum. The subgroups contain several functional groups important in maintaining orthorhombic lateral packing, which allows tight apposition of lipids and creates a highly waterproof structure. Ceramides also play a crucial role as a signaling interface between hydrophilic corneocytes and lipophilic extracellular lipid matrix. Unlike triglycerides and wax esters, ceramides contain amide linkages analogous to those found in protein (Figures 2B and 4C). These bonds are also hydrolyzed by alkali.

### Cellular Injury

Alkalis saponify phospholipid-based cell membranes leading to cell rupture and death, while the cation (eg, sodium ion) allows deeper penetration. Saponification proceeds as for triglycerides with the hydroxide ion attacking the ester bonds, to release the two fatty acid chains from the glycerol molecule, while facilitating alkali metal cation replacement of the fatty acid proton (soap).

### Protein Denaturation

Proteins are formed in the free cytosolic ribosomes as well as those on the surface of the rough endoplasmic reticulum when mRNA brings coded individual amino acids in proximity to the growing peptide chain under manufacture. The associated peptide bonds form on reaction between the carboxylic acid group (–COOH) of one amino acid and the amine group ($-NH_2$) of another with the loss of water (Figure 2B). Alkalis hydrolyze or break peptide bonds, resulting in disruption of structure and function. This denaturation results in "liquefaction" of the protein—conversion from large three-dimensional structures into much smaller and more soluble components. Sugars attached to glycoproteins can also be removed under these conditions. When the agent has a pH >11.5, the liquefactive necrosis exposes deep tissue planes to alkali attack.[9] Deep penetration ceases when all of the hydroxide ions have been consumed, or when there is no additional tissue with which to react.

## CLINICAL SIGNS AND SYMPTOMS

The first clinical sign is an early "greasy" or "soapy" texture detected when touching the affected skin, which is caused by fat denaturation and fatty soap formation. This is followed by progressively worsening pain caused by epidermal cell death and inflammation secondary to cell membrane phospholipid denaturation and serial tissue injury. Pain worsens as dermal protein structures are similarly denatured, including vascular elements, causing dermal necrosis. Tissue liquefaction potentiates deeper invasion and progressive necrosis and subcutaneous fat saponifies and facial or muscular protein is denatured.

## FIRST-AID OPTIONS

First-aid is important in reducing the injury severity after alkali exposure. In each case, the important clinical outcome is the cessation of the subjective sensation of "burning." Once the alkali has been removed or inactivated, the patient will state that the "burning" has stopped, the area will remain "sore" instead. If the "burning" sensation cannot be stopped, even after prolonged irrigation, surgical excision should ensue. There are four possible first-aid methods of dealing with alkalis on skin.

### Dilution by Water Irrigation

The old adage "the solution to pollution is dilution" holds true. Irrigation with running water is the most frequently applied first-aid method in South Australia. In most large industrial settings, pressure-activated showers enable rapid access to large volumes of running water. Additional advice includes irrigating "to the floor," ensuring that the "run off" does not cross uncontaminated skin or structures. This is especially important with facial alkali exposure, if uninjured eyes are to remain that way after irrigation! Animal studies suggest that irrigation must commence immediately, or within a minute of injury; delayed irrigation (after 10 minutes) has no effect on pH changes in the subcutaneous tissues and by extension on the degree of tissue destruction and injury severity.[14] Because of the liquefactive effect of alkalis, this immediate irrigation needs to be prolonged compared to thermal burns, and even

other chemical agents such as acids. Irrigation for up to 2 hours is recommended. Because such irrigation is for decontamination, not burn wound cooling, it can be warmed so that prolonged irrigation does not cause hypothermia in extensive chemical injury.

### Neutralization

Neutralization infers the restoration of a neutral pH (7.0) by the inactivation of an alkali with a weak acid, or an acid with a weak alkali. While the idea appears to have merit from a chemistry standpoint, the historical issue marring widespread adoption is the potential of the neutralizing agent to cause additional skin injury. Such injury might result from overzealous application of the neutralizing agent pushing the pH past neutral, or by the heat generated by the acid-base reaction (which is exothermic). However, the use of acetic acid (a weak acid because of its reticence to ionize and release its proton) after sodium hydroxide skin exposure has been studied, apparently with positive results.[15] However, in industrial settings, running water is likely to be more readily available than a first-aid station where neutralizing agents are available, especially since most large industries use a range of different chemicals, including both alkalis and acids. Other concerns center around "which neutralizing agent to use for which chemical" when it comes to educating the general public. In such situations, the certain benefit of immediate washing with water from the tap outweighs the potential benefit of better outcome from neutralization if decontamination is likely to be delayed while the victim reads first-aid information on the chemical container to ascertain the appropriate neutralizing agent!

### Buffering

Our intracellular and extracellular fluids are maintained at a nearly constant pH, irrespective of metabolic changes that might occur. The reason is because biological buffer systems exist to deal with the additional production of protons or hydroxide ions. The two main biological systems are the phosphate buffer and the carbonic acid or hydrogen carbonate buffer. The principle is that the buffer system contains both a hydrogen ion donor and a hydrogen ion acceptor in equilibrium, so that the buffer system itself remains at neutral pH.

$$\underset{\text{(Proton donor)}}{H_2PO_4^-\,(aq)} \rightleftharpoons H^+\,(aq) + \underset{\text{(Proton acceptor)}}{HPO_4^{2-}\,(aq)}$$

In the above equilibrium, if additional hydroxide ions enter the extracellular fluid, they will react with the $H_2PO_4^-$ (monobasic phosphate), shifting the equilibrium to the right. Additional protons will react with the $HPO_4^{2-}$ (dibasic phosphate) shifting the equilibrium to the left. In both situations, the pH of the system is unaltered. Such buffers can be employed therapeutically and buffer solution eyewashes containing monobasic and dibasic sodium phosphates in equilibrium are available for first-aid use to combat both alkalis and acids. Buffering on the skin is less effective than water irrigation in the immediate exposure period, but where presentation is delayed by 10 to 30 minutes, buffers may have some value where no first-aid has been previously applied.[16] However, delayed treatment of *any* kind in alkaline skin exposure invariably results in severe injury.

### Amphoteric Chelation

Diphoterine™ is a recently introduced, commercially available, amphoteric, chelating molecule presented in an aqueous, hypertonic, polyvalent washing solution. The molecule has different active sites capable of binding both protons and hydroxide ions, making them unavailable for reaction with tissue. It is expensive and must be employed within seconds of exposure. Thus, such agents have found use in major industry as "belt packs" (100 ml personal aerosols) for immediate use.[17] This represents the only new addition to the first-aid tools for alkali skin exposure.

## CONCLUSIONS

The chemical processes outlined above help to rationalize the aggressive behavior of alkaline hydroxides on contact with key biomolecules such as lipids and proteins in human tissues. While we read and learn about these processes during our education and training, occasional reiteration is useful. Revision makes us better educators and also underlines the urgency required in advising referring clinicians, in on-site decontamination and in treating injuries involving these hazardous agents.

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