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Syndets in the Treatment of Atopic Eczema

Cleansing of Eczematous Skin - The Scope of the Problem

The idea of cleansing human skin is a comparatively old one. In fact cleansing agents of the soap type have been in use for at least 4500 years. We know from a written document from Tello that long before Christ the Mesopotamians managed to prepare soap from oil and wood ash [55]. The need of skin cleansing using some type of cleansing agent nowadays seems to be obvious to a wide majority of people, at least in industrialized countries. Although the need to cleanse the skin also seems to be common knowledge among dermatologists [42], this need is astonishingly ill defined in scientific terms. In fact, recent reviews on skin cleansing agents concentrate by and large on unwanted but not wanted effects [61-63]. Certainly one has to keep this in mind when it comes to the role of syndets (or soap) in the treatment of atopic eczema. The use of syndets for skin cleansing in general does largely go back to the problem of cleansing eczematous skin [6].

„Most dermatologists agree that the skin of patients with atopic eczema should be kept clean". [68]. This belief is comparatively well substantiated by clinical and experimental findings and especially applies to the removal of endogenous dirt (crusts, scales etc.) which obviously are always present. Indeed, the aim of skin cleansing is to remove both endogenous and exogenous dirt, especially considering the workplace. Patients with atopic eczema can react to the intracutaneous injection of human dander with an itching wheal reaction and to the occlusive epicutaneous application (48-h patch test) with an itchy eczematous reaction, as has been demonstrated by Uehara and Ofuji [66, 67] thus substantiating older observations [24, 58]. Debris on eczematous skin such as scales, moreover, might promote [68] the growth of Staphylococcus aureus, whose role in the aggravation of the disease has been stressed recently [30].

Despite this rationale for thorough cleansing of eczematous skin, as early as in the thirties dermatologists came to the conclusion, in view of the side effects of the cleansing agents available at that time, that patients with eczema should not use soap. In a fundamental paper from 1930 Stauffer [59] writes: „it

seems to be justified to draw the conclusion from these results that the type and chemical condition of the various soaps in general does not influence the development of eczema on a large scale. Individuals, however, prone to the development of eczema should best avoid soap because of the enormous risk of eczematous reaction. For this reason I now forbid the use of soap with almost all of my patients with occupational eczema. I have had good experience in doing so." This approach, which in the German-speaking countries is referred to by the widely used term "Seifenverbot" (no soap) later found many proponents.

This is easily understood, considering the irritant effect of soap even on normal skin, an effect which became evident during the following decades [4]. As early as 1937 Rostenberg and Sulzberger [46] were also able to demonstrate using the patch test that soap irritates the skin of patients with atopic eczema more often than others. Thus "no soap on affected areas" has, for example, become part of the holistic approach towards the management of atopic eczema, which in the United States of America (USA) is known as the "Scholtz regimen" [2, 52, 53]. As with most treatment modalities for atopic eczema the concept of prohibiting the use of soap in patients with atopic eczema has not remained unchallenged [60]. In an open trial Uehara and Takada [68] were able to demonstrate improvement of eczema in patients complying to a protocol of conventional topical therapy for atopic eczema when they started having regular shower baths with common toilet soaps after having refrained from skin cleansing before. Today common text books still advise against a deliberate use of soap. Braun-Falco, Plewig and Wolff [9], put it this way: "The asteatotic skin tends to dry out and itch. Repeated and prolonged baths with the use of alkaline soaps or foam baths should be avoided".

In short, up to the advent of chemical alternatives to conventional soaps the dermatologist treating patients with atopic aczema had to decide for himself either to advocate the regular use of soap in order to prevent the possible adverse effects of dirty skin, accepting the potential risk of severe irritancy, or just the opposite.

The Development of Synthetic Detergents - A Real Option

In chemical terms skin cleansing agents are amphiphilic substances, i. e. substances comprising both hydrophobic and hydrophilic moietes. When added to water such substances disperse in a certain way. In particular they become arranged in an orderly way at surfaces such as water to air. These substances interact with substances which are only slightly soluble in water, e. g. dirt, and solubilize them, making it easier to rinse them off after washing. It is this effect of soaps which is employed both for washing textiles amd human skin. In the USA such substances are still sometimes called detergents. Yet there is now almost general agreement to speak of surfactants instead [55]. Up to the beginning of this century soap, i. e. a mixture of alkali salts and fatty acids, was the only surfactant available for cleansing both textiles and skin.

In 1928, however, Bertsch and Schrauth for the first time synthetized fat alcohol sulfates [55]. The introduction of such synthetic detergents, or, to put it more correctly, surfactants, soon revolutionized the field of textile cleansing. At the end of the Second World War synthetic surfactants almost completely replaced conventional ones within a single decade [57]. During this time synthetic surfactants were also introduced in Germany in textile cleansing, not least by a Koblenz-based manufacturer called Maurer. And, in fact, his younger brother, who as a pediatrician was confronted with the problem of cleansing eczematous skin, was one of the first to promote the idea of also using the new substances to cleanse the skin, especially so-called problem skin [6].

Dermatologic evaluation of the new products was primarily performed by Keining [23] at the dermatology clinic in Mainz. While he still used the term syndet in a more general sense, it is largely due to his work that in a stricter sense syndets are now defined as products composed of synthetic surfactants used for cleansing the skin primarily of the hand or foot and face region. Thus, from a chemical standpoint similar products used for showers etc. are excluded [55]. While soap as a rule is available as a bar, the first syndets were liquid, which primarily seemed to prevent widespread acceptance. Therefore syndet bars were also developed. "Rei" was among the first to be developed, by Maurer, and was clinically evaluated by Keining. In a fundamental paper Keining [23] described various properties of the new cleansing agents:

1. Syndets are more efficient than soaps in removing dirt and bacteria from human skin. As this is linked to their emulsifying properties skin lipids necessarily are also removed to a greater extent, and the skin becomes rougher because its water binding properties are influenced.

2. Syndets other than soaps do not sensitize, hence eczema-prone patients can be allowed to use syndets under certain circumstances.

3. Syndets do not bind calcium and magnesium . This would otherwise lead to deposits which cause itch and then give rise to exacerbation in eczema-prone patients, and so these individuals may use syndets.

4. Syndets can be acidified. In particular it is possible to adjust a pH of 5.7 to 6.0 in order to protect the acid mantle of the skin. This also prevents the swelling of the epidermis seen when soap is used.

Keining added a list of various skin diseases to his paper, thus forming the base of the later concept of syndets as basic treatment (in German so-called Basistherapie; [7] in skin diseases. Keining himself, however, did not include atopic eczema here.

Although fat alcohol sulfates are still frequent ingredients of syndet preparations, a variety of different components and compositions has been developed in the meantime. From a chemist's point of view the major advantages of syndets are:

1. They can be used in hard water. Thus chalk soaps do not result and neither the cleansing capacity nor the potential for foam production are debilitated.
2. The pH can be selected and the skin can be cleansed with a neutral or slightly acidic product.
3. Syndets are compatible with many additives. This makes it possible to meet special requirements [55]. Synthetic detergents can either contain anionic, nonionic, or amphoteric ingredients. Anionic surfactants comprise sulfates such as fatty alcohol sulfate and fatty alcohol ether sulfate, sulfonates such as sulfosuccinate and carboxylates such as sarcosinate (as well as soap) and phosphates such as alkyl phosphate. Nonionic surfactants comprise polyglycol ethers as well as polyglycol esters and fatty acid alkanolamides. A typical representative of amphoteric substances is alkyl betaine [51]. For chemical details see Table I.

As syndets are mixtures of various chemicals the composition is of utmost importance. Although nowadays general principles are known to the public, and although ingredients are often declared according to the CTFA recommendations, the desirable and undesirable effects of commercial preparations cannot be derived from readily available information. In fact, dermatologic judgement is made even more difficult as commercial preparations are subject to frequent change. The principles of available preparations are described in more detail in a recent review [49].

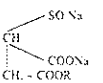
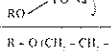
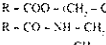
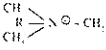
Type of Surfactant	Congener	Formula
Anionic		
Sulfates	Fatty alcohol sulfate	$R-CH_2-OSO_3Na$
	Fatty alcohol ether sulfate	$R-CH_2-O-(CH_2-CH_2-O)_2-SO_3Na$
Sulfonates	Sulfosuccinate	
	Methyltauride	$R-CO-N(CH_3)-CH_2-CH_2-SO_3Na$
Carboxylates/ phosphates		
	Sarcosinate	$R-CO-N(CH_3)-CH_2-COONa$
	Alkyl phosphate	$RO-PO_3Na_2$ 
Nonionics	Polyglycolether	$R-O(CH_2-CH_2-O)_2H$
	Polyglycolester	$R-COO-(CH_2-CH_2-O)_2H$
	Fatty acid alkanolamides	$R-CO-NH-CH_2-CH_2-OH$ 
Amphoterics	Alkyl betaine	
	Alkylamidopropyl betaine	

Table I Major representatives of the various types of surfactant used in syndets and their chemical structure [modified from 51].

Desirable and Undesirable Effects of Syndets on Human Skin - the Role of the pH

Commercial syndet preparations still have high cleansing activity compared to soaps. This does not only apply to normal skin but also to the affected parts of the skin of patients suffering from atopic eczema. Seemingly, the differences between the cleansing capacity of a syndet such as Sebamed and a soap such as Lux are even greater when it comes to eczematous skin [71]. This at least can be derived from experiments with a frequently used skin washing machine devised to remove a staining model dirt [54].

As early as in 1928 Schade and Marchionini [48] published the results of determinations of the skin surface pH giving data ranging from 3.0 to 5.0. As early as that they spoke of an acid mantle ("Säuremantel") and attributed to it a role in the regulation of the bacterial microflora on the skin surface. This concept was further substantiated in three consecutive papers entitled: "Säuremantel der Haut und Bakterienabwehr" (Acid mantle of the skin and protection from bacteria) 10 years later [32-34]. This has been the subject of much controversy up to the present time. The older standpoints are well described by the following statements: According to Pillsbury and Rebell [39] "The hypothesis of an 'acid mantle' as a principal factor in making the skin a less favorable area to support the growth of microorganisms has gained wide acceptance. This hypothesis is dependent upon the fact that the surface of normal unabraded skin has been shown by many observers to have a low pH. It has also been shown that intertriginous areas have a somewhat higher pH, and the conclusion was drawn that this higher pH was therefore the principal reason for localization of infection in intertriginous areas". According to Cornbleet [10] "there is no proof in the literature nor do my experiments support the hypothesis that the self-sterilizing powers of the skin are due to the surface acid". During the last decades many independent research workers have found a skin surface pH in the range 5.4-5.9, i.e., a mean value of about 5.5 [8]. Some, however, still hold the belief that the mean skin surface pH is not close to pH 5 but between pH 6.4 and 6.5 [62]. Although Tronnier is still a proponent of this hypothesis, he and Bussius [64] reported a mean value of pH 5.8 in a large field trial. In fact, the debate on the true skin surface pH has in the meantime resulted in the creation of syndets with a pH of 7.0 considered in terms of irritancy to be superior to slightly acidic ones [37].

Marchionini et al.[34] were the first, but not the only ones, to demonstrate a relationship between the pH of the habitat of skin bacteria and their growth. While they were able to demonstrate differences in the growth of Bacterium prodigiosum (today called Serratia marcescens) on the skin surface of the forearm claimed to be acidic and the skin surface of the axilla claimed to be alkaline, the fungistatic effect of the fatty acids found in human sweat, in particular of undecylenic acid, was found to be the highest at a pH of 5.0 (as compared to 5.6, 6.0 and 7.0) [14], caprylic acid was found to be more active against Staphylococcus aureus at a pH of 4 (instead of 5) [35], and the so-called

water-soluble components of the stratum corneum were able to kill both Staphylococcus aureus and coagulase-negative staphylococci ("Staphylococcus albus") at a pH of 5, but not a pH of 7 or 8 [44, 45]. The idea of the influence of the skin surface pH on skin bacteria is further backed by recent findings from in vitro experiments. While Staphylococcus aureus distinctly showed optimum growth at pH 7.5 Propionibacterium acnes grew best at pH 6.0 and pH 6.5. Thus minor shifts from pH 5.5 to pH 6.0 may markedly promote the growth of P.acnes while the same might not be true with stapylococci [26]. In addition, the pH of the external environment seems to influence the enzymatic activity of skin bacteria. At least the lipase activity of „Corynebacterium acnes" (Propionibacterium acnes) is said to be double at a pH of 7.0 as compared to 5.1 [15].

As to optimum pH of skin cleansing preparations, an influence on the human skin microflora, however, can only be expected if cleansing agents can in fact influence the skin surface pH for a substantial amount of time. Yet this has been questioned repeatedly up to the present time. Long-term observation of the influence of repeated washing with various agents on the skin surface pH are scanty. It was mainly Pösl and Schirren [40] who in earlier days contributed to the discussion of the problem. They came to the conclusion that even repeated washings with alkaline soap do not influence the skin surface pH in the long run although it is moved towards the alkaline within the first hours following each individual washing procedure. Interestingly, this conclusion is, however, not completely backed by experimental findings they referred to. In fact, in the morning before the skin was washed again, it was still somewhat more alkaline than before the start of the systematic washing procedures. The idea of just a temporary influence of alkaline cleansing preparations on the skin surface pH most recently has been virtually substantiated by our own experimental findings. Rieger [43] and Proksch [41] quote the short-term results of a controlled trial in normal human volunteers, showing that after the application of (alkaline) soap the skin surface pH first moves from baseline values by about two pH units followed by a return to about the initial value within about 120 min. Yet they do not quote the additional finding that during the trial performed over 8 weeks on the whole the mean pH in the group using the acidic syndet (Sebamed liquid) was lower by 0.3 pH units than in the group using (alkaline) soap (Lux) [27]. This difference, which in other terms means that three times as many free hydrogen ions are available on the skin surface when the acidic syndet is used repeatedly, correlates with a marked difference in the density of propionibacteria but not coagulase-negative staphylococci. As to be expected from the in vitro findings cited above propionobacteria, but not staphylococci, were significantly more abundant when alkaline soap, not acidic syndet, was used regularly. More recently, these findings were substantiated by further trials. When syndets of almost identical chemical composition except for the pH were used, corresponding differences were found comparing a preparation of pH 5.5 with another one of pH 7.0 [28]. The latter investigation clearly demonstrates that it is the pH value of the cleansing preparation, and not the various components, which actually influence the skin surface pH and, hence, its microflora.

This seems to deserve all the more interest as a shift to the alkaline is one of the features of affected and seemingly unaffected skin in patients suffering from generalized exczema [12]. Only the findings concerning the skin roughness after the repeated application of several chemically different syndets with acidic or neutral pH values hinted at a superiority of the neutral ones in terms of irritancy [37]. Therefore most recently both roughness of the skin surface and transepidermal water loss (TEWL) were examined on repeated application of syndet preparations differing only in their pH. In controlled trials the preparation of pH 5.5 was always compared with the more alkaline one either of pH 7.0 or 8.5. Though both parameters always increased during the trial period, there were no definite differences between the various groups while this was again the case with respect to the skin surface pH [29]. The lack of a clear-cut relationship between the pH of the syndet preparation and its potential for irritancy found here corresponds well to earlier findings. As early as in the sixties Tronnier, Schneider, Schuster and Modde [65] drew the conclusion from pertinent experimental work that: "The side effects (undesired secondary effects of the tensides) are to a very slight degree pH dependent. However, side effects tend to increase with the elevation of pH values.". This is in clear contrast to Schneider's [50] earlier belief that syndets should be slightly alkaline in order to be less irritant. Most recent investigations based on the 48-h application of sodium lauryl sulfate under occlusion showed that this ionic surfactant, formerly a major ingredient of syndets, does not increase TEWL if the pH of the preparation lies at 5 or 7, while it does so to a certain extent at a pH of 9 [1].

Although the pH of a syndet preparation might not have a major influence on the side effects, there is scientific basis for believing that a chemical preparation could cleanse human skin without compromising its barrier function in any way [41]. The permeability barrier of human skin is primarily composed of cornifying keratinocytes which are rich in protein and the intracellular substance which is rich in lipids. The intercellular lipids are particularly important as they are able to influence both trans- and paracellular permeation. In the keratinocytes which form the stratum spinosum, the lamellar bodies known as keratinosomes are composed of lipids. These bodies are liberated within the stratum granulosum, providing the upper parts of the epidermis with lipids of lamellar arrangement. These lipids, epidermal lipids, are different from sebum lipids [11]. Another major constituent of the upper parts of the epidermis is water. Its concentration in the uppermost parts of the epidermis, however, is much lower than in others. The mixture of epidermal lipids, sebum lipids, water, salt, and organic acids forms a system which has been interpreted as a water-lipid mantle or natural moisturizing factor [41].

As skin cleansing, by definition, means removal of xenobiotics deposited on the skin surface and emulsified by the water-lipid mantle and of body secretions such as sebum or sweat or other body products such as scales, it is harmful to the epidermis. The practical question, however, is to what extent. In fact, syndets are not necessarily less harmful with respect to irritancy. The clinical dermatologist who had become familiar with "soap dermatitis" by

the end of the 1940s [21] was confronted with a new type of "detergent dermatitis" at the beginning of the 1950s in various parts of the world. In Sweden this was due to a syndet called "Original X," containing, apart from other ingredients, 6% lauryl sulfate. Irritancy has soon chased back to this anionic surfactant.

During the last decades the irritant potential of various surfactants being considered as possible ingredients of syndets has been evaluated by different methods comprising the Duhring chamber test. In particular these studies have identified the comparatively high irritant potential of sodium lauryl sulfate [22, 72]. Sodium lauryl sulfate increases the TEWL. Increased TEWL, a typical feature of so-called dry skin, is even higher in patients with atopic eczema than in normal individuals [70]. Sodium dodecyl sulfate applied repeatedly also increases skin roughness. This effect is linked to its adsorption to human keratin layers [19]. Decreased stratum corneum hydration and increased roughness of the skin surface are linked to changes in the composition of epidermal lipids. While the total amount of lipids is not altered, the ratio of free cholesterol to cholesterol ester is increased. The total amount of ceramides is not significantly changed either after the application of sodium dodecyl sulfate, yet the amount of one particular ceramide is, i. e. ceramide 3 [17]. In fact, those intercellular lipids which are depleted are able to reconstitute those water-retention properties needed to keep the skin supple when sodium dodecyl sulfate is applied [20].

Fortunately, other surfactants influence TEWL less than sodium lauryl sulfate. This, for example, applies to sodium laurate [70]. Today, it is common knowledge that one has to look both for the irritant potential of any single possible ingredient as well as at that of the complex mixture when it comes to the evaluation of a cleansing product to be made commercially available [69]. It is no longer justified to assume that efficacy and tolerability of a skin cleansing preparation are closely linked. In a recent trial comparing various commercially available soaps and syndets one particular soap, i. e. Purpose, ranked first with respect to its cleansing capacity but only fourth with respect to irritation potential. In the given context, however, it might be more important for a syndet bar to rank first for its low irritation potential though it is the least effective in terms of cleansing the skin [38]. It is obvious today that no general statement can be made as to the safety of syndets or soaps. Due to a chamber test especially devised for the evaluation of skin cleansing preparations one representative of the syndet group, i. e. Dove, ranked first while another syndet preparation. Zest, ranked almost last (16th of 18) [16]. Definite evaluation of a skin cleansing modality has also to be based on results of long-term application under practical conditions, i. e., on in-use properties [47]. According to the results of a recent trial of that type, irritancy is most marked during the first weeks of regular application [31]. Moreover, the relative increase of side effects does not seem to be greater in individuals prone to atopic disease. Yet this does not preclude the occurrence of clear-cut detergent eczema as shown in Fig. 1 even with most recent syndet preparations.

Fig. I.
Irritant dermatitis in an atopic due to the frequent use of a syndet bar representing "detergent eczema"

Syndets and Eczematous Skin - Clinical Assessment

Controlled trials on the desirable and undesirable effects of syndet washings on the normal and affected skin of patients with atopic eczema seemingly do not exist. According to an open trial applying an acidic syndet (pH-5-Eucerin Lotio) twice daily for 14 days to involved or uninvolved skin of 60 patients with eczema, among them 12 with atopic eczema this preparation is well tolerated both on affected and healthy skin [25]. Faulhaber and Lechner [13] found an acidic syndet (i. e. Sebamed flüssig Waschemulsion) helpful in 22 of 30 female patients with eczema. Yet the syndet was applied in a bath. Schwarz [56] described a supportive effect of the use of syndets in patients with occupational eczema presumably at least in part linked to atopy. The scanty inconclusive experimental results on the effect of syndets on the skin of patients with atopic eczema compared to soaps corresponds to the lack of definite evidence whether the application of soap to eczematous skin really does major harm. Neither Brain [5] nor Bettly [3] found soap to be injurious when applied regularly to cleanse eczematous skin of infants.

Hence, further clinical trials of the following design are needed: An adequately large cohort of patients with manifest atopic eczema is graded clinically [18]. Each subject is attributed to one of a total of three subgroups at random. In a modified double-blind fashion each trial participant receives either soap, a syndet, or nothing at all for skin cleansing. The latter group is asked to totally refrain from washing their skin. The other subgroups are asked to use their cleansing agent twice daily before the application of the other treatment modalities for eczema. These treatment modalities are the same for all subgroups. During the entire trial period of 10 days one type of medium-potent

glucocorticoid cream is applied in the evening, followed by the corresponding vehicle in the morning. The state of skin is investigated on days 5 and 10 using the same grading scheme as at start. Corresponding to the usual application of a soap or syndet, the skin areas should be cleansed using a diluted solution for 30 sach and then rinsed with plain tap water. Such a trial would probably clarify whether the inherent harm brought about by the application of a cleansing agent is less than the advantage of removing the dirt from the skin. Moreover, we would know whether soap or syndet are superior if cleansing agents are indeed indicated in the management of atopic eczema.

If this is to, the differential judgement on soap and syndets, respectively, has to take into account that both represent a large variety of compositions of various chemicals substances. This applies even more so to syndets. Thus, for example, the pH of syndet preparations can be selected freely. While at present the ultimate skin cleansing preparation for eczematous skin may not be available, this might be the case in the near future. In fact, it would not astonish us if it were a syndet.

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