 doi:10.20944/preprints202002.0360.v1

# Controlling Systemic Inflammation By Careful Formulation of Topical Skin Care Products: Our Bodies Didn't Evolve With All the Current Chemicals in Skin Care Products

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*Preprints* (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 February 2020 doi:10.20944/preprints202002.0360.v1

**Abstract**

Although man is still rapidly evolving, he has not co-evolved with all of the modern chemicals made by man, including those in cosmetic products. Care must be taken when formulating products so that commonly used ingredients, such as polyethylene glycol, can be substituted with safer ingredients to which man has adapted and that will not cause irritation and inflammation. This is especially important given that induction of skin inflammation will cause systemic inflammation. A review of the literature and of commercially available products was made to highlight techniques and products that remediate inflammation or induce inflammation. Many skin care products contain chemicals that induce irritation and inflammation that may lead to chronic, systemic inflammation. Well studied natural products, especially skin identical chemicals, may offer an advantage compared to recent man-made chemicals in cosmetic and topical formulations and help to reduce skin inflammation as well as skin derived systemic chronic inflammation.

**Key Words:** Skin care, topicals, toxicity, ingredients, systemic inflammation

## Background

Man is still evolving, but he has not co-evolved with all of the modern chemicals made by man, including those classified as nanomaterials (Nel et al, 2005). In the USA, as of 2011, there were 83,000 chemicals on the market without proper regulation for safety (Vogel and Roberts, 2011). About two thousand new chemicals are made each year. Of the small subset of chemicals that have been tested, pharmaceutical ingredients for example, toxicologists working with regulatory agencies mainly analyze acute health effects, with few tests of chronic exposures, and the epigenetic transgenerational effects not considered (Xin et al, 2015). Skin cancer, for example, has been demonstrated in an animal model of transgenerational epigenetic inheritance when the grandparent but

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not the grandchild was exposed to atrazine, a commonly used herbicide (McBirney et al, 2017). Barrier disruption (Fluhr et al, 2005) and atopic dermatitis (AD) may result from many of these exposures to the skin (Kim, 2015; Kantor and Silverberg, 2017). Simple barrier disruption, such as through tape stripping, leads to the release of inflammatory cytokines, an up to five-fold increase in the expression of MHC class II antigens, activated Langerhans cells, a type of macrophage-dendritic cell hybrid (Doebel et al, 2017) and induced T cell proliferation (Katoh et al, 1997). In turn, inflammatory cytokines, but probably not inflammatory T cells (Shams et al, 2017), in the skin can spread systemically (Ye et al, 2019) leading to a number of inflammatory conditions, such as a proatherosclerotic macrophage phenotype, leading to macrophage cholesterol crystal formation, with impaired SOD2 function associated and accelerated atherogenesis (Baumer et al, 2018). Evidence for the role of chemical exposure as a causative factor in atopic dermatitis comes from epidemiological and experimental studies. For example the doubling in lifetime prevalence of both atopic dermatitis diagnosis [from 13.9% (1995–96) to 27.2% (2001–02)] and atopic dermatitis symptoms [from 8.8% (1995–96) to 19.6% (2001–02)] in boys aged 13–14 in England (Shamssain, 2007) is likely to represent a true change in prevalence and environmental factors are likely causative (Deckers et al, 2012). Our exposome likely accounts for 70-90% of chronic diseases (Smith and Rappaport, 2010). In response to our exposures, the immune system is a learning system like the brain (Rook et al, 2017). In one aspect, having evolved to anticipate data input from our symbiotic microorganisms (microbiota), and ingested and topical chemical exposures that are particularly abundant in the gut and skin, and from organisms and chemicals in the natural environment, modern lifestyles have decreased and distorted these inputs. This distortion of symbiotic inputs, including those from non-commensal bacteria and man-made chemicals, contributes to failing regulation of the immune system. Failing immunoregulation contributes to increases in chronic inflammatory disorders, such as allergies, autoimmune disease and inflammatory bowel disease, where the immune system is targeting things it should not attack. As humans co-evolved with microbial communities and chemicals (those eaten in plants for example), many microbial products and chemicals were co-opted to play roles as signals for the development and function of essentially all organ systems,

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including the brain (Dalile et al, 2019). It was not possible to build a sufficient repertoire of receptors to recognize a vast and rapidly changing array of microbial molecules by simply duplicating receptor genes and evolving variants. This would have added enormously to the size of the genome and yield a response that is too slow. Such a mechanism could never keep up with microbial evolution and the manufacture of new chemicals. Therefore the “adaptive” immune response appeared. Invertebrates, with their simpler microbiotas, do not have this type of adaptive immune system. Part of the mechanism depends on exposure to as many microorganisms and natural chemicals as possible. Thus the adaptive immune system develops a repertoire that is relevant to the microbial and chemical environment in which the individual lives, rather than to a microbial and chemical environment from the distant past, but to develop this repertoire it must have an “educational” input of microorganisms and chemicals from the gut and the environment. The first influenza virus infection during the first three years of childhood, termed immune imprinting, is recognized for its influence on subsequent infections and vaccinations (Kelvin and Zambon, 2019). The early imprinting event initiates a cascade of innate and adaptive immune responses, including from T cells (Nelson and Sant, 2019), leading to an immunological memory retained over a person’s lifetime.

The adaptive immune system generates a vast repertoire of receptors (antibodies for example) by mutation, so few genes are required. Thus a new repertoire is generated de novo in each individual. Then lymphocytes bearing relevant receptors are selected and clonally expanded, while useless ones, or any that recognize the individual’s own tissues, are eliminated.

Given that most of our diseases result from our exposome (Rapapport, 2016), the argument is put forth that physicians need better education in epidemiology, an interrogative epidemiological database, and better diagnostic tools for discovering a patient’s exposome (Rapapport et al, 2014). For example, pollution, including the widespread industrial class of hydrocarbons known as dioxins, can activate Th17 cells through activation of the aryl hydrocarbon receptor (Veldhoen et al, 2008), enhancing

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inflammatory responses. These inflammatory responses induced by dioxin can be exacerbated by co-treatment with retinoic acid leading to increased skin lesions (Rudyak et al, 2018). Retinoic acid is commonly used for a number of skin conditions, including acne. Part of the exposome, along with exposure to foreign chemicals in the environment, are our own stress induced chemicals such as cortisol and prolactin. Stress, acting through increased cortisol production can impede protein synthesis and wound healing (Christian et al, 2006). Likewise, stress can cause increased levels of prolactin (Lennartsson and Jonsdottir, 2011). Recently discovered in keratinocytes is that prolactin enhances their proliferation (Girolomoni et al, 1993), and interferon-gamma-induced production of (C-X-C motif) ligand 9 (CXCL9), CXCL10, and CXCL11. Therefore prolactin may promote plaque formation and Th1 cell infiltration into stressed skin through the actions of these chemokines (Kanda and Watanabe, 2007). While the focus of this paper is on chemical exposure to the skin, psychological stress may help to trigger or exacerbate the effects of the chemicals (Vesterinen et al, 2017). For example, mast cells in the skin are activated by stress that produce stress hormones and inflammatory factors. This activation may lead to a vicious cycle of stress-induced inflammatory events associated with acne, atopic dermatitis, psoriasis and pruritus (Arck et al, 2006). Likewise, exposures of what we ingest can have profound effects on the skin. Fiber, for example, can reset the function of T cells (Trompette et al, 2018), cells that are important in the AD sequlae (Auriemma et al, 2013), and indeed, fiber can reduce the symptoms of AD (Gruber et al, 2015).

A heredity component, including possible genetics, has also been associated with AD. Considering genetics, with a population explosion where man has expanded by at least three orders of magnitude over the past 400 generations (Keinan and Clark, 2012), selection is dwarfed by the effect of genetic drift in human populations (Eaaswarkhanth et al, 2016). With this drift and lack of selection, human diseases may negatively affect fitness but fail to be eliminated from the population. There are thousands of relatively common disease-susceptibility variants in modern human populations. A small portion of common genetic variants yield relatively large phenotypic effects that remain in the human population, as exemplified by the FLG LoF variants of fallagrin. FLG is one of the primary loci that has been associated with atopic dermatitis (AD). The fitness

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advantage of not being susceptible to the FLG LoF mediated disease appears not to be high such that even extant, wild chimpanzees carry the LoF variant too (Eaaswarkhanth et al, 2016). Reduced fillagrin function will lead to disorganization of the stratum corneum and resultant trans epithelial water loss (TEWL), and irritation and pruritus (Gruber et al, 2011). With the explosion of population growth also comes an increasing exposure of human beings to novel pathogens, particularly the crowd infections that were not part of our evolutionary history (Rook et al, 2017).

In the context of skin inflammation inducing systemic inflammation (Ye et al, 2019), a cormorbidity has been described for AD with rheumatoid arthritis (RA) and irritable bowel disease (IBD), and the authors (Schmitt et al, 2016) speculate that the development of RA and IBD in subgroups of patients with AD is precipitated by a sustained skin inflammation with increased TH1/TH17 signaling and secretion of proinflammatory cytokines including TNF-α, similar to what has been postulated for a subgroup of patients with psoriasis. The authors suggest that epigenetic changes secondary to prolonged systemic inflammation might be another mechanism linking chronic-inflammatory diseases. Schmitt et al (2016) did not find a higher proportion of established risk alleles for IBD and RA nor was T1D associated with AD in a consistent directionality more frequently than the 50% expected by chance, indicating that these diseases do not have a shared genetic background. However, the immune abnormalities observed in AD are in part predetermined by heredity, including a genetic component, as evidenced by established AD susceptibility genes that regulate T-cell differentiation and effector function, or encode components of the innate immune system (Barnes, 2009). Thus, exposure-mediated inflammation of the skin in AD results in an increased probability of comorbidity from IBD and RA.

As humans coevolved with plants and ate a diet rich in vitamin C we lost our ability to make vitamin C. Compared to other genes, the *GLO* gene for making vitamin C was susceptible to being lost because the gene makes a single compound, and is unnecessary for the synthesis of other molecules (Linster et al, 2007). Only the loss of vitamin C is incurred with the loss of this gene. Therefore, with a high intake of plants and their vitamin C, primates no longer needed to make vitamin C and eventually lost

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the genetics to make that one molecule, and only that one molecule. Normal skin contains high concentrations of vitamin C similar to other tissues, and because it is dietarily derived, vitamin C is transported into cells from the blood vessels present in the dermal layer (Pullar et al, 2017). More vitamin C is found in the epidermal layer than in the dermis, with differences of 2–5-fold between the two layers reported (Rhie et al, 2001). Vitamin C levels are lower in aged or photodamaged skin. Excessive exposure to oxidant stress by pollutants or UV irradiation is associated with depleted vitamin C levels in the epidermal layer (Shindo et al, 1994)

Important to the skin barrier, vitamin C enhances the late differentiation of keratinocytes, overcomes the oxidative stress induced by differentiation, and maintains the integrity of the stratum corneum (Ponec et al., 1997; Savini et al., 2002). One study of vitamin C in atopic dermatitis demonstrated a reduction in serum levels of vitamin C that correlated with the severity of AD (Shin et al, 2016). No such correlation was found for vitamin C levels in the epidermis. Unfortunately the study made no comparison of vitamin C levels in the epidermis on control subjects, and so evidence as to whether the vitamin C levels in the epidermis of AD patients are normal or not was not presented. The benefits of topical vitamin C application are numerous. For example, a 10% ascorbic acid (water soluble) and 7% tetrahexyldecyl ascorbate (lipid soluble) formula was shown to decrease wrinkles and increase collagen production in a clinical trial (Fitzpatrick and Rosten, 2002). In clinical studies, vitamin C-containing topically applied solutions have been shown to reduce UV-induced thymine mutations, thereby potentially reducing the risk of photocarcinogenesis (Murray et al, 2008). A number of other benefits have also been observed for topically applied vitamin C (Al-Niami and Chiang, 2017). Thus, the topical application of a coevolved molecules, vitamin C, is beneficial to the skin.

A recent NY Times article (Sanders, 2019) written by a physician details the life threatening episodes one man had in severe reaction to a common chemical, PEG, found in pharmaceutical products, skin care products, personal lubricants, and as a food additive, that resulted in anaphylaxis. Without an epipen and subsequent emergency room visit, the patient would have died. Topical application of PEG led to an immediate skin reaction in this patient. The episodes he experienced with one chemical represent

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the broader problem of modern man's exposure to thousands of man- made chemicals to which our bodies have only recently been exposed in evolutionary time, and therefore potentially harmful chemicals to which we have not evolutionarily adapted, and that may be leading to diseases such as cancer (David and Zimmerman, 2010). Importantly, new research shows that inflammation in the skin will translate to blood borne systemic inflammation (Ye et al, 2019). Age and diet induced inflammation have been linked to many chronic diseases, including Alzheimer's disease, cardiovascular disease, and diabetes (Christ and Katz, 2019). Scientists have provided evidence that this inflammation originates from the immune system and the liver and gut (Sochoka et al, 2019), but now the largest organ in the body has been implicated. Ye et al (2019) studied thirty-three older adults between the ages of 58 and 95 who applied a lipid-based emollient cream over their entire bodies twice a day. At one month into the study, the blood levels of three cytokines, interleukin-1 beta, interleukin-6, and tumor necrosis factor (TNF) alpha, were measured. These factors have been implicated in age-related inflammatory diseases and mortality (Lee et al, 2012). Using the cream reduced the amount of the three cytokines compared to the participants' levels before using the cream, and also reduce the levels of the cytokines of similarly aged adults who did not use the cream. The cream was so effective that the regimen lowered participants' inflammatory cytokine levels to that of people in their 30s, suggesting that epidermal repair can reverse systemic inflammation. This study suggests that formulation of a topical skin care product can not only control inflammation in the skin, but also systemically and therefore care is required in the choice of topical products and their ingredients to be administered to patients.

## Methods

The ingredients of a number of skin care products were examined for their potential irritating and inflammatory effects, or ingredients that may lead to positive, anti-inflammatory effects in the skin.

## Results

### Examples of Potentially Harmful Chemicals in Skin Care Products

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Although humans are still evolving, and maybe evolving faster than before (Pennisi, 2016), our evolutionary processes can't keep up with the addition of new chemicals that are constantly being made. In the case above, the culprit was the recently invented PEG, polyethylene glycol. Considering other ingredients, let's look at the example of one topical skin care product, AnteAge Serum, promoted by an anesthesiologist and currently on the market and positioned for sale to estheticians, physicians, and other health care providers:

Ingredients: Water/Aqua, Human Bone Marrow Mesenchymal Stem Cell Cytokines, Niacinamide, Cetyl Ethylhexanoate, Dimethyl Isosorbide, Polyacrylate-13, Glycerin, Hydrolyzed Myrtus Communis Leaf Extract, Ilex Paraguariensis (Mate) Leaf Extract, Carnosine, Butylene Glycol, Carbomer, Palmitoyl Oligopeptide, Palmitoyl Tetrapeptide-3, Polyisobutene, Polysorbate 20, Tetrasodium EDTA, Sorbic Acid, Benzyl Alcohol, Salicylic Acid.

The ingredient list on this product contains a number of questionable chemicals, of which a number have better alternatives. First, butylene glycol is known to cause allergic contact eczema in humans when topically applied to the skin, characterized by an immediate immune response (Magerl et al, 2003; Aizawa et al, 2014; Stone et al, 2018). Butylene glycol (1.3-Butanediol) is a small organic alcohol used as solvent and conditioning agent derived from petroleum. Glycols are diol molecules consisting of two -OH groups attached to a hydrocarbon chain, whereas alcohols have one –OH group. In contrast to alcohols and glycerin, these types of glycols are synthesized and not found in nature. The parent molecule of the glycols is ethylene glycol (EG) and is extensively used in industry, including as a solvent in cosmetics.

Second, although cetyl ethylhexanoate is considered to be safe for use in skin care products when diluted, the chemical itself causes irritation of the skin (Fiume et al, 2015) and therefore as a stay-on, constantly used skin care chemical, may induce inflammation. Third, carbomer has been shown to be cytotoxic when applied to the skin (Guo et al, 2015). Fourth, in one study of polyisobutene, in vitro application was shown to promote a cancer-like cellular transformation (Cosmetic review panel, 2008). Fifth, polysorbates have been demonstrated to irritate the skin and cause an immediate

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immune response, especially when co-applied with glycol (Stone et al, 2018). Sixth, the secretome from the bone marrow stem cells (BMSCs) is harmful in many ways, including the induction of a classic M1 inflammatory response with release of cytotoxic chemicals, fibrosis, stem cell exhaustion (Maguire, 2019), and dangerous cellular proliferation (Luo et al, 2014) caused by an activation of mTOR for example, and the resulting promotion of head and neck cancer (Liu et al, 2018). The use of BMSC secretome in combination with polyisobutene may induce an especially proliferative, cancer-like state in the skin. Instead of the proinflammatory cytokines from bone marrow stem cells, the use of adipose derived mesenchymal stem cells and fibroblasts provides a proresolving, anti-inflammatory set of cytokines and other molecules for use in skin care therapeutics (Maguire, 2019). Seven, most cosmetic products will need preservative systems unless they are an anhydrous formulation, with those systems often being cytotoxic and irritating, potentially damaging the cells, including fibroblasts in the skin (Spindola et al, 2018). While preservatives are necessary for non-anhydrous formulations that are not packaged in sterile, single use containers, care must be used in the choice of the preservative to be used. For example, the use of common preservatives including parabens (Seo et al, 2017, Kizhedath et al, 2019), benzalkonium chloride (Baudouin et al, 2010), and to a lesser extent phenoxyethanol (Gallo et al, 2005; Dinkloh et al, 2014) has been questioned, often with limited evidence (Kirchhof and de Gannes, 2013), and safer alternatives are being explored. One new preservative class are the antimicrobial peptides (AMP), naturally derived from biological organisms such as bacteria and with fewer negative side effects to the host (Matsuzaki, 2009). One such AMP is nicin, naturally synthesized from *Lactococcus lactis,* and approved for use as a food preservative in the EU. Mauricio et al (2017) have shown nicin to be an effective preservative for topical skin care products when used with other preservatives, with the addition of nicin serving to lower the effective concentration of the other synthetic preservatives. Other AMPs, such as bacteriocin KT11, are being explored and have demonstrated a broader range of antimicrobial activity, and reduced sensitivity to heat and pH compared to nicin (Abanoz and Kunduhoglu , 2018).

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Let's consider two topical skin care products from "RxGenesys by Jeffrey Gibson MD," that are being promoted by a surgeon. Their RxMoisturizer product has the following ingredients:

Water, Candelilla/Jojoba/Rice Bran Polyglyceryl-3 Esters/Glyceryl Stearate/ Cetearyl Alcohol /Sodium Stearoyl Lactylate, Capric/Caprylic Triglycerides, Glycerin, Cetearyl, Induced Pluripotent Stem Cell Extract, Dimethicone, Butylene Glycol,Dextran/Caprooyl-Tetrapeptide-3, Polygonum Aviculare Extract, Tetrahexyldecyl (Vitamin C), Tocopheryl, Vitamin E, Hyaluronic Acid, Green Tea, Pro-Vitamin B5, Hydroxyethylcellulose, Xanthan Gum, Phenoxyethanol /Caprylyl Glycol/Ethylhexylglycerin/Hexylene Glycol

And their RxVital product has the following ingredients:

Deionized Water, Induced Pluripotent Stem Cell Extract, Glycerin, Butylene Glycol, Glycerin (and) Water (and) Dextran (and) Caprooyl-Tetrapeptide-3, Water (and) Glycerin (and) Polygonum Aviculare Extract, Tetrahexyldecyl Ascorbate (Vitamin C Ester), Tocopheryl Acetate (Vitamin E Acetate), Hyaluronic Acid, Camellia sinensis (Green Tea) Leaf Extract, Panthenol (Pro-Vitamin B5), Hydroxyethylcellulose, Lactic Acid, Polysorbate 20, Phenoxyethanol (and) Caprylyl Glycol (and) Ethylhexylglycerin (and) Hexylene Glycol, Fragrance.

The most harmful ingredient is the purported use of "induced pluripotent stem cell extract" in both products. Pluripotent stem cells (abbreviated as iPS or iPSC) are not ready for therapeutic development due to many problems (Tapia and Scholer, 2016), especially given their genetic and epigenetic reprogramming errors (Liang and Zhang, 2013; Lister et al, 2011) resulting in, amongst other abnormalities, their secretome inducing cancer and fibrosis (Rosner et al, 2017), and potentially containing misfolded proteins that are associated with Alzheimer's Disease (Hu et al, 2018). Epigenetic imprinting is disturbed in the reprogramming process, independent of the original state of the cell to be reprogrammed (Perera and Martello, 2019), and can be a contributing cause of cancer (Bartolomei and Ferguson-Smith, 2011). Furthermore, using an extraction process to collect the molecules from the iPSCs will lead to damaged molecules, including damaged, non-functional proteins (Lillford, 1983) as well as

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damaged, misfolded proteins (Chen et al, 2011) that may have toxic prion-like characteristics (Prusiner, 2013; Maguire et al, 2019). The extraction process can be contrasted to the methodology where the molecules are released from the cells, often packaged into exosomes, where the molecules, including proteins are in their fully formed tertiary or quaternary state without loss of function and gain of toxicity, prion-like characteristics. The exosomes released from adipose derived mesenchymal stem cells, for example, contain heat shock proteins that will protect and help to refold proteins and elicit positive effects in their target cells (Liu et al, 2019). As in the previously discussed product, polysorbates have been demonstrated to irritate the skin and cause an immediate immune response, especially when co-applied with glycol (Stone et al, 2018). Like the misuse and overuse of stem cell transplants, where the cell types used for transplant and the risk versus reward are not being properly evaluated by many physicians (Maguire, 2018b), careful consideration of the cell type, processing of the cells for molecule collection, and formulation with other ingredients must be made to prevent harmful topical skin care products from reaching the market in general, and the clinic in particular where, for example, immune impaired patients may be put at risk by the product.

**Examples of Potentially Therapeutic Chemicals in Skin Care Products**

The stratum corneum is the principle UV filter in Caucasian skin (Kaidbey et al, 1979), and the barrier to water loss and penetration of irritants into the skin (Kezin and Jakasa, 2016). When the stratum corneum is perturbed, it is a leading cause of atopic dermatitis (van Smeden and Bouwstra, 2016). Moreover, hitherto unknown was that inflammation in the epidermis alone will give rise to systemic inflammation in humans (Ye et al, 2019).Lets consider products that use skin identical or skin biomemtic ingredients to restore barrier function mediated by the stratum corneum.

Recently a product (NTP-CE, Bepanthen®SensiDaily) was shown to restore barrier restoration as measured by TEW. The ingredient list is:

Aqua, Caprylic/capric triglyceride, Glycerin, Olea europaea fruit oil, Isostearyl isostearate, 1,2-hexanediol, Cetearyl alcohol, Panthenol, Butyrospermum parkii butter,

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Niacinamide (vitamin $B_3$), Glyceryl stearate citrate, α-glucan oligosaccharide, Limnanthes alba seed oil, Hydrogenated lecithin, Hippophae rhamnoides fruit extract, Tocopheryl acetate, Xanthan gum, Sclerotium gum, Squalene, Tetrasodium glutamate diacetate, Ceramide 3, and Citric acid.

Key to the success of this product in restoring barrier function and hydration of the stratum corneum (Stettler et al, 2017) is using a combination of skin biomemetic ingredients that mimic the composition and multilamellar structure of stratum corneum of a 1:1:1 molar ratio of free fatty acids, cholesterol, and ceramide (Mao-Qiang et al, 1996) using the 1:1:1 ratio to restore barrier function. However, to optimally restore barrier function using exogenous lipids, a 3:1:1 or a 1:3:1 ratio was found to work equally well (Mao-Qiang et al, 1996), and restore the barrier more quickly than using the 1:1:1 molar ratio of lipids. Pseudoceramides such as Myristoyl/palmitoyl Oxostearamide/arachamide MEA (Park et al, 2000) can be used in place of natural ceramide. Properties of physiological lipid-based products are different from nonphysiological agents, such as petrolatum. Physiological lipids are taken up by keratinocytes, packaged into lamellar bodies, and then secreted to form lamellar bilayers. Treatment with non-physiological lipids such as petrolatum (Vaseline), lanolin, and beeswax, do not enter the lamellar body secretory pathway but rather fill the extracellular spaces of the stratum corneum with hydrophobic non-lamellar lipid that inhibits the movement of water and electrolytes (Ghadially et al, 1992). The non-physiological petrolatum lipids can very rapidly, but only partially restore barrier function (Elias, 2006). Another disadvantage of non-physiological lipids is that they also can inhibit the normal permeability barrier repair mechanisms and thus not repair the underlying abnormality in lamellar structure (Elias, 2006).

**Example of Misinformation in Skin Care Marketing**

Some confusion seems to exist among practicing physicians about the best formulations for restoration of the barrier function using exogenous lipids. For example, Leslie Baumann, M.D. in her blogs writes, “Myristoyl/palmitoyl oxostearamide/arachamide mea is a pseudoceramide that uses multi-lamellar emulsion (MLE) technology to mimic the natural organization of lipids within healthy human skin”

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(http://lesliebaumannmd.com/myristoyl-palmitoyl-oxostearamide-arachamide-mea-mle-technology-is-the-best-barrier-repair/). And in a Miami Herald article, Dr. Baumann writes, "the skin barrier needs a 1:1:1 ratio of ceramides, fatty acids, and cholesterol." She further states that, "Multi-lamellar emulsion (MLE) technology refers to the use of a topical formulation that very closely mimics the natural lamellar structure of the lipids in healthy human skin. Studies have shown that MLE formulations can effectively restore the barrier function of your skin. All of her statements are incorrect. First, Myristoyl/palmitoyl Oxostearamide/arachamide MEA is a pseudoceramide that provides one of the three necessary lipids to fully restore the barrier. This ingredient alone does not create the MLE. And second, whether the ratio of 1:1:1 she describes is based on molarity or mass, the 1:1:1 is not needed, and is indeed, suboptimal (Mao-Qiang et al, 1996). Measuring the time to recovery of barrier function (TEWL), if one of the ingredients was used at a 3:1:1 molar ratio, especially cholesterol (Zettersten et al, 1997), then both parameters were significantly improved compared to the 1:1:1 ratio of the three lipids. Further, there is currently no data to suggest that an MLE formula works better than the same ingredients that have not been processed into an MLE. Such control studies have not been published. Although Atopalm, an MLE formula, was shown to be more efficacious than Physiogel Intensive Cream, a non-MLE formula, the results are likely due to differences in the composition of ingredients, including a very different set of lipids (Jeong et al, 2016). In another study, (Sul et al, 2013), drug delivery of a topical steroid (desonide) was measured using an MLE versus a non-MLE formula. The authors conclude, "Topical desonide formulation using MLE as a vehicle showed a better drug delivery with increased epidermal retention. MLE also partially prevented the steroid-induced side effects, such as skin barrier impairment" (Sul et al, 2013). However, if one reads the study, the MLE formula was compared to a formula that contains a very different set of ingredients (see Table 1 in Sul et al), including sodium laurel sulfate, an ingredient known to disrupt barrier function as shown by increased TEWL, erythema, and increased inflammatory cytokines (De Jongh et al, 2006). In order to understand whether the MLE is partially responsible for the restoration of barrier function, the same ingredients in an MLE formula versus a non-MLE formula would need to be tested. Although Baumann may be confused about the

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lipid technology, the company she has set up (skintypesolutions.com) does sell a product (Zerafite Barrier Repair Moisturizer) that is in-licensed from NeoPharm, one of the companies that does create an efficacious physiologic lipid technology (Atopalm), and where Byeongdeog Park, Ph.D. created the Myristoyl/palmitoyl Oxostearamide/arachamide MEA, and formulated the product with consultation from Mao-Qiang Man, M.D. and Peter Elias, M.D of UCSF (Ye et al, 2019). Unfortunately, although NeoPharm advertises their MLE as something very efficacious, there are no published studies supporting the MLE per se as providing benefit, and the Zerafite product contains a number of ingredients that are potentially harmful.

The ingredients in the Zerafite barrier restoration cream:

Water, Glycerin, Butylene glycol, Cetearylalcohol, PEG-15 glycerol stearate, Vitis vinefera (Grape seed) oil, Glycerol stearate, Macadamia ternifolia seed oil, squalane, stearic acid, PEG-10 glycerol stearate, Sodium lacta portulaca oleracea extract, Biosaccharide gum-1, Myristoyl/palmitoyl oxostearamide/arachamide MEA, Tocopher acetate, Glycyrrhiza glabra (Licorice) root extract, Dimethicone, Sunflower oil decyl esters, Cholesterol, Methylparaben, Carbomer, Propylparaben, Allantoin, BHT, Fragrance.

A number of the ingredients in the Zerafite product are potentially harmful to skin health. The problems with PEG were already highlighted, and include anaphylactic shock when ingested (Shah et al, 2013; Lee et al, 2015) and severe allergic reactions with elevated IgE levels and the presence of PEG antibodies (Povsic et al, 2016). Further, contact allergy to fragrance is widespread (Bennike et al, 2019), butylenes glycol may induce contact dermatitis (Diegenant et al, 2000; Tamagawa-Mineoka et al, 2007; Aizawa et al, 2014), and stearate's use in topical skin care products has been questioned by a group of dermatologists at UCSF because of its proinflammatory actions (Li et al, 2018) through induction of a number of proinflammatory cytokines (Miao et al, 2015). The use of methylparaben and propylparaben in cosmetic products is widespread (Guo and Kannan, 2013), and are present in the urine of over 90% of those tested despite rapid metabolism of the parabens (Calafat et al, 2010). Using epidemiological and experimental studies, parabens induce or are associated with a number of health

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issues, including thyrotoxicity (Vo et al, 2010), induction of a genetic stress response (Garcia-Espineira et al, 2018), earlier thelarche, menarche, and pubarche (Harley et al, 2019), and possible oncogenic effects (Wróbel and Gregoraszczuk, 2015). Thus, the inclusion of deleterious ingredients may overcome the benefits of the three lipid types in this formula.

Included in these formulations for barrier function restoration is the essential fatty acid, linoleic acid, a long chain fatty acid that is required for structural barrier formation (Jeong et al, 2016). Thinking in terms of coevolution, let's consider the linoleic acid component. As man evolved to eat mostly plants, high consumption of essential nutrients, such as linoleic acid, may relax selective pressures on an organism to maintain autotrophy (Ellers et al, 2012) for this fat is found abundantly in dietary plants. For example, linoleic acid is the main component of the soybean membrane (Zhuang et al, 2017). However, man didn't evolve to consume high levels of linoleic acid during the neonatal period, a time when breast milk is the main nutrient. Relatively high levels of linoleic acid consumption as a neonate, such as that when fed formula instead of breast milk, is associated with an increased risk of lymphoblastic leukemia (Petrick et al, 2019). Such research highlights the need for understanding the evolutionary and developmental aspects of medicine, where, in the study of Petrick et al, a molecule with which we coevolved as something to be consumed as an adult is destructive when consumed as a neonate. High oxygen therapy for premature neonates that led to a generation of retinopathy of prematurity (retrolental fibroplasia) is another classic example of how important an understanding the evolutionary and developmental aspects of our exposures is to the development of medical procedures and products, including drugs (Hartnet and Lane, 2013).

Other skin identical ingredients of use in restoring barrier function include urea. Urea is present in the lipid lamellar system at all levels of water content in the stratum corneum to protect against lipid lamellar disassembly even during dry conditions (Pham et al, 2018), and is a well described humectant used in various topical emollients that has been very recently shown to normalize barrier function and antimicrobial peptide (LL-37

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and -defensin-2) expression in a murine model of AD (Grether-Beck et al, 2012). Urea is an endogenous metabolite that is actively transported into the skin (Grether-Beck et al, 2012). A commercial skin barrier restoration cream (Balneum cream) containing 5% urea along with the three lipid types (free fatty acids, cholesterol, and ceramide) has been shown to have positive effects on barrier function and corneum stratum structure in aged subjects with dry skin (Danby et al, 2016). Although the 5% urea is an effective moisturizer, important to the barrier restoration effect of this product is the proper lipid content. Elias and Sugarman (2018) have stressed the importance of not confusing moisturization with barrier restoration. Indeed, moisturization alone without proper barrier restoring ingredients can be toxic to sensitive, or otherwise compromised skin.

Another molecule we coevolved with is butyrate, a short chain fatty acid produced by commensal bacteria on our skin (Christensen and Bruggemann, 2014), that regulates immune function, including the programming of macrophages (Schulthess et al, 2019). Using this molecule that we coevolved with, Schwarz et al (2017) showed that topical butyrate can modulate Treg function such that hapten induced skin inflammation was significantly reduced. One product on the market that contains the three necessary lipids, urea, and butyrate is Barrier Renewal Cream by NeoGenesis Inc.

**Discussion**

The exposome accounts for about 70-90% of our chronic diseases (Smith and Rappaport, 2010; Rappaport, 2016). The exposome includes many new and untested chemicals that, along with rapid genetic drift and lack of selection, and the modern environment that precludes functional training of the adaptive immune system, has led to a rise in many health conditions, including atopic dermatitis. In particular, topical skin care products often contain ingredients that were unknown to humans as we evolved, such as PEG and polysorbate. Skin care products may also contain natural ingredients at concentrations that we didn't evolve with, or natural ingredients that did not evolve to be in contact with our skin. This includes ingredients that are biologically derived, such as the "Induced Pluripotent Stem Cell Extract" derived from genetically modified human cells in an extraction process, yielding a potentially dangerous cancer causing and prion-like set of molecules. This also includes the biomolecules derived from BMSCs

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that are normally only present in the skin during brief episodes of significant wounding. If applied to the skin frequently, the BMSCs derived molecules will induce inflammation, proliferation, and resident stem cell exhaustion (Maguire, 2019). High levels of natural oils if not formulated into a proper mix of the necessary lipid types to maintain barrier function can induce inflammation. As such, many of these new chemicals, or the use of chemicals in an unnatural manner, most of which have not been thoroughly tested, may have negative side effects in man. Therefore, the argument is advanced that natural products, those that have evolved with man and are used in a manner in which they evolved, including proper use during man's developmental stages (recall the aforementioned problems with linoleic acid in neonates but not adults) and have been thoroughly studied, may best serve skin health and consequently systemic health. Moreover, given that we evolved an adaptive immune system that requires training early in life, the modern world with its limited number of natural organisms and its altered sets of chemicals, leads to exposure to chemicals with which we have not adapted. Thus natural products that are not skin identical, and to which we have not adapted, may induce an allergic reaction. As example, skin identical ingredients that serve as humectants, urea and glycerol (Bjorklund et al, 2013), the lipids ceramide, linoleic acid, and cholesterol that build the lipid structure of the stratum corneum (Mao-Qiang et al, 1996), and the biomolecules derived from skin resident (and its fat pad) stem cells that induce pleiotropic effects in the dermis and epidermis (Maguire, 2019), may provide a distinct advantage when formulating topical products for the skin. The overall idea is to develop a systems therapeutic (Maguire, 2014), where multiple molecule types target multiple pathways underlying the disease or condition, to develop physiological renormalization, where the set of molecules present in the normal state of the tissue are provided to diseased tissue to restore normal physiology (Maguire et al, 2019). A physiological renormalization strategy has been successfully used to develop "checkpoint inhibitors" that induce physiological renormalization of the adaptive immune system so that T cells can once again attack cancer cells (Sanmamed and Chen, 2018), a technology for which the 2018 Nobel Prize in Physiology or Medicine was awarded. Using a systems therapeutic for physiological renormalization is under development to treat neurodegenerative disease (Maguire et al, 2019; Maguire, 2019b), and was

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successfully used by Mao-Qiang et al (1996) to develop products containing multiple lipid types (systems therapeutic) to mimic and restore barrier function (physiological renormalization) of the stratum corneum with a resulting reduction in skin and systemic inflammation (Stettler et al, 2017; Ye et al, 2019).

**Conclusion**

A bewildering array of skin care products are on the market. The bewilderment is amplified by misleading information concerning these products, often promulgated by healthcare professionals. Evidenced based skin care products, formulated and produced in a manner consistent with developing a “systems therapeutic” for “physiological renormalization” are currently on the market and provide a means for quelling skin inflammation and resultant systemic inflammation.

**Abbreviations**

AD – atopic dermatitis

BMSC- bone marrow stem cell

CXC - CXC-type chemokines

EG - ethylene glycol

FLG – filaggrin

IBS – irritable bowl syndrome

LoF – loss of function

MHC- major histocompatibility complex

MLE – multilamellar emulsion

PEG - polyethylene glycol

RA - rheumatoid arthritis

TEWL – transepidermal water loss

**Consent to Publish:** Not applicable

**Availability of Data and Materials:** Not applicable

**Competing Interests:** Dr. Maguire has equity in NeoGenesis Inc.

**Funding:** Not applicable

**Ethics approval and consent to participate:** Not applicable

**Acknowledgements:** Not applicable

**Author Contributions:** GM is solely responsible for this paper.

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