

2018

**HIGH-DOSE TAURINE WITH
LOW-DOSE MAGNESIUM
FOR THE TREATMENT AND
PREVENTION OF ACNE**



Shape Scientific, LLC
White Paper

HIGH-DOSE TAURINE WITH LOW-DOSE MAGNESIUM FOR THE TREATMENT AND PREVENTION OF ACNE

A Shape Scientific, LLC White Paper with the special goal of trying to halt acne at its early onset in life, before it becomes serious or chronic

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The essential ideas and research presented in this White Paper form the basis of U.S. Patent No. 9,795,633 [Issue Date: Oct 24, 2017; Inventor: Margaret Profet]. This U.S. Patent was licensed in 2018 to Shape Scientific, LLC.

ABSTRACT/SYNOPSIS:

Acne is still considered to be an unsolved problem both academically and clinically. Acne of some degree afflicts almost 100% of people, usually in the teenage and young adult years, and sometimes earlier in childhood or later in adulthood. Acne can become chronic, with large negative impact on quality-of-life.

High-dose taurine supplementation in combination with low-dose magnesium supplementation appears to clear mild to moderate (noncystic) acne 90% – 100% within 4-14 weeks in adults, and it may significantly alleviate some cases of more severe acne with longer treatment, according to results of a small informal volunteer study. The purpose of this paper is to explore mechanisms-of-action and other fundamental information for the investigation of oral and topical high-dose taurine with low-dose magnesium as treatment for acne in a large diverse population. A special purpose also is to spur action to try to halt acne at its first onset in youth via early intervention, for example by using high-dose taurine with low-dose magnesium supplementation as soon as acne first shows up on the face of a child, or even earlier as a possible way to prevent acne.

The lines of reasoning in this paper are summarized as follows:

Acne (*vulgaris*) is a disease characterized by a clogging of the skin's pilosebaceous units—consisting of the sebaceous glands, sebaceous ducts, and attached hair follicles—by the lipids (sebum) produced by the sebaceous glands. A major cause of clogging is excess lipogenesis in the sebaceous glands, leading to excessive number and/or size of sebaceous lipid droplets.

The main idea of this paper is that sufficient taurine and magnesium in the pilosebaceous units helps keep the sebum at low enough volume and at fluid enough flow to prevent clogging. A relevant finding from the taurine literature is that the pilosebaceous units of animals accumulate taurine at high density when ample taurine is made available to the body.

The pilosebaceous units appear to have natural anti-acne design features that use taurine and magnesium when both these micronutrients are present in the pilosebaceous units in sufficient amounts. These are the two main mechanisms-of-action:

- 1) Taurine very likely helps stop excess sebaceous lipogenesis, by binding as an inhibitory ligand to the receptors of the type LXR-alpha (liver X receptor-alpha) expressed by cells of the sebaceous glands. The LXR-alpha of sebaceous cells and other cell types usually induces lipogenesis when activated by ligands, but taurine has already been shown in vitro in human liver cells to be an LXR-alpha ligand that inhibits LXR-alpha-induced lipogenesis.

2) Magnesium very likely triggers the breakdown of the large lipid droplets in the sebaceous glands and ducts to micro-lipid droplets and usable lipids via magnesium-activated protein kinase A phosphorylation of the lipid droplet surface protein perilipin A. Phosphorylation-activated perilipin A has been shown in adipose cells to fragment the lipid droplets into many micro-lipid droplets and disperse them, and in various cells to recruit lipase enzymes to break down the lipid droplets to usable lipids. Magnesium is the activator of protein kinase A phosphorylation. Such action in the sebaceous glands/ducts, whose lipid droplets express perilipin A, should help prevent excessive size and clustering of lipid droplets and the consequent clogging of the sebaceous ducts and hair follicles.

The switch by humans from the hunter-gatherer way of life to the agricultural way of life resulted in a dietary intake of taurine that has been, for most agricultural humans, chronically suboptimal, and a dietary intake of magnesium that has been often suboptimal. Although some taurine is synthesized internally, humans depend on dietary taurine to maintain optimal levels. Taurine in human diets comes almost exclusively from animal tissues. It is at high levels in many meats/fish and in human breast milk but is virtually absent in plant foods and low in cow's milk. According to anthropologists cited in this paper, agricultural humans on average have eaten much less meat/fish as a percentage of their diets than did ancestral hunter-gatherers. Meanwhile, dietary factors that have been shown by some researchers to exacerbate hormone-driven sebum production, such as high glycemic load, have greatly increased in agricultural societies. Thus, taurine intake has likely decreased, while the need for it to counter sebum production has increased. Magnesium deficiency is also very common in agricultural diets, due in part to decreased variety of plant foods in individual diets and reliance on refined foods.

According to the biomedical literature on the “thrifty phenotype hypothesis”, which applies to fetuses and infants, and the “triage theory”, which applies to persons or animals of all ages, if the body detects a chronic shortage of a particular micronutrient, it allocates the micronutrient primarily to tissues most critical for survival, at the expense of tissues of secondary importance. In the case of taurine, for example, even a modest chronic shortage might lead to a patterned down-regulation of the taurine transporters in the pilosebaceous units, tissues of secondary importance in humans, leading to serious taurine shortage there. Of relevance is that the intake of taurine early in life—in fetal period via the transfer of taurine from the mother to the placenta, in infancy, and in babyhood—has probably been less for most agricultural humans than it was for ancestral hunter-gatherers. The domestication of animals, for example, has allowed cow's milk to be substituted for taurine-rich human breast milk for babies. Early-in-life taurine insufficiency might have a pronounced long-term effect on the pilosebaceous units. In order for the body to route ample taurine to the pilosebaceous units after a long period of taurine deficiency, it may need to detect a surplus of taurine. Taurine shortage in the pilosebaceous units appears to be reversible by high-dose taurine supplementation. Magnesium shortage in the pilosebaceous units appears to be reversible by relatively low-dose supplementation.

Information in some parts of the paper focuses more on taurine than on magnesium because currently more data relevant to the development of acne seems to be available regarding taurine than magnesium. It should be emphasized, however, that the acne treatment proposed depends on the dual actions of taurine and magnesium—i.e., the simultaneous operation of both the taurine-driven and magnesium-driven anti-acne mechanisms in the pilosebaceous units. Taurine and magnesium are also somewhat synergistic.

Preliminary evidence that high-dose taurine supplementation combined with low-dose magnesium supplementation can clear or significantly alleviate acne was obtained from a small group of adult volunteers with acne. The effective daily doses for average-weight adults with mild/moderate acne are 3g taurine with 200-300 mg magnesium, in divided doses, taken on an empty stomach, for several weeks or months. These doses are believed safe and have virtually no side effects. Subsequent lower maintenance doses may prevent acne from returning. Adults with severe acne may require a higher taurine dose or a much longer treatment time for good clearing. The effective doses for children should vary according to weight of the child and degree of acne.

Topical taurine-magnesium gel treatment, once developed, might penetrate the pilosebaceous units more quickly and be even more effective than oral treatment. Taurine topically applied to human skin samples in experiments has been shown to penetrate deeply into the dermis. Magnesium (especially magnesium chloride) topically applied to human skin samples in experiments has been shown to permeate skin mainly through the hair follicles—the route to other parts of the pilosebaceous units and the route that may be ideal for treating acne—as well as through the stratum corneum. Combination oral and topical taurine-magnesium treatment might provide maximum benefit in serious cases of acne, countering it simultaneously from the inside-out and the outside-in.

PART I: INTRODUCTION

Acne, Although Almost Ubiquitous Among Humans, is Not a Natural Part of the Human Condition

(Author's Note: Although many parts of this paper are highly technical, this introduction begins with a brief explanation of why I explored the subject of acne and how I came up with the idea of high-dose taurine with low-dose magnesium supplementation for acne.)

Initially in Pursuit of a Simple Understanding of the Puzzle of Acne, Decades Later By Chance I Came Upon a Potential Clinical Solution

The phenomenon of acne previously did not make sense to me, and it does not seem to make sense to most acne patients or their dermatologists. One of the striking and puzzling aspects of acne is that it afflicts almost 100% of persons to some degree, at some stage of their lives, primarily during teenage and young adult years. Acne's visible toll on youth is huge: at any given time, most teenagers seem to be experiencing acne—68% of 12-17 year-olds in one large door-to-door 1976 U.S. government study (Roberts, 1976). In 1986 or 1987, after delving into a study of evolutionary physiological puzzles, I studied the subject of acne for a brief time because it seemed like a different type of puzzle, unnatural from the context of evolution, due to the following irony: the main occurrences of acne in a person's life span the peak physical "beauty years"—acne mars or even disfigures youth, exactly the phase of human life that the human brain is designed to see as the most physically beautiful. This extreme mismatch between simultaneous repulsion to acne pustules and attraction to physical correlates of youth does not make adaptive sense. Doubting that ancestral humans who lived the most evolutionarily natural way of life—the hunter-gatherers—would have been afflicted with acne, I called up anthropologist Marjorie Shostak, who had just returned from one of her Kalahari Desert studies of hunter-gatherers, and I asked her whether she recalled ever seeing any acne on any hunter-gatherers; but she responded that she did not think she could have distinguished acne from bug-bites. At the time, I investigated acne for only a short while, saw no solution to either the academic puzzle of acne or to the clinical problem of it, and gave up studying acne until 2013, when I noticed from personal experience a surprising link between the micronutrient taurine and skin condition.

In 2012 I studied taurine for a few weeks while working with biochemist Bruce Ames (of Children's Hospital Oakland Research Institute) on his project of analyzing various dietary micronutrients within the framework of his triage theory, about how the body re-allocates micronutrients during periods of micronutrient deficiency (see Ames, 2006). Taurine stood out as especially interesting to me in that it is used biochemically by the body in so many different ways and forms, which is probably why dedicated taurine scientists referred to it as a "Wonder Molecule".

Useful starting facts about taurine include, for example: Taurine is an amino sulfonic acid, often referred to as a “free” amino acid because it is not incorporated into proteins, and present in perhaps all mammalian cells. Taurine has many known functions and probably many unknown functions. Its main overall function seems to be as an osmolyte, regulating cell water volume (Huxtable, 1992); as such, it facilitates the transport of certain ions, especially sodium, potassium, and magnesium, across cell membranes (Human Metabolome Database). Taurine also helps modulate calcium flux, which affects contractile response in heart and muscle (Huxtable, 1992). It also has surfactant and detergent actions, by conjugating to bile acids in order to form bile salts that emulsify dietary fats (Huxtable, 1992). It has antioxidant actions when it binds to chloramine produced by neutrophils, modulating the immune system in ways that help shut down the cascade of pro-inflammatory cytokines (Schuller-Levis and Park, 2004). And it is critical for the fetal development of brain and retina (Sturman et al, 1978). These are just some examples of how taurine is needed.

Taurine is synthesized internally to some degree by all animal species. In mammals taurine is primarily synthesized from cysteine via a pathway involving the enzymes cysteine dioxygenase 1 (CDO1) and cysteine sulfinic acid decarboxylase (CSAD) (UniProtKB, 2016), although there are multiple pathways for synthesis, some involving methionine and vitamin B-6 (Huxtable, 1992; Wojcik et al., 2010). Taurine is present in animal tissues and so can be obtained in diet from meat/fish and milk. Dairy contains a variable amount of taurine, depending on the species of dairy animal.

Because my vegetarian diet contained no meat or fish, I figured that my taurine level was suboptimal, so in early 2013 I began taking oral taurine supplements. I was already taking a low-dose multivitamin/mineral that contained magnesium. The effect on my skin of supplementing with taurine was so beneficial that I paid more attention to the situation. Understanding taurine as osmolyte, I suspected that it might be working with one of the mineral ions in cells in a way that cleared skin, and I guessed magnesium over the other ions. Experimenting personally with supplements and doses, I found that if I stayed on a low maintenance dose of taurine and magnesium, sporadic acute hints of “problem” skin were cured rapidly with a 2-day spike in supplemental taurine dose combined with an increased supplemental dose of either magnesium or multivitamin/mineral pills containing magnesium.

Wondering in early 2014 if taurine with magnesium could improve acne conditions in people generally, I started investigating the biomedical literature to find out why taurine with magnesium might have anti-acne effects on skin. I also started recommending high-dose taurine plus low-dose magnesium, taken with water on an empty stomach, to acquaintances with acne, with dramatic results. (I could not convince Bruce Ames to join me at all in this project, as he was immersed in his own important scientific projects. So I soloed it, then later went looking for potential partnerships.)

In the first couple of days of my academic investigation into acne, I thought about my decades-earlier call to anthropologist Marjorie Shostak and wondered if anyone in the intervening time had ever gone out and done a study on hunter-gatherers and acne, so I searched Medline. As it turned out, Shostak's colleague S. Boyd Eaton had conducted such a field study, with a team led by Loren Cordain (Cordain et al, 2002). Their pivotal study is described further below. The gist of their findings confirms that acne is not a natural part of the human condition.

Seeing acne as a phenomenon of the post-hunter-gatherer rather than the natural way of life opens up possibilities for new approaches to understanding the etiology of acne and to treating acne in the modern world.

The Research Strategy for this Paper has been to Identify Natural Anti-Acne Mechanisms and their Triggers in the Pilosebaceous Units

The research strategy for this paper at first entailed sifting extensively through the biomedical literature to 1) look for ways in which taurine with magnesium might possibly help unclog the pilosebaceous units of the skin; and 2) see what is experimentally known about the etiology of acne and the biology and physiology of the macroscopic and microscopic structures involved. Then the research strategy suddenly switched to 3) setting aside the focus on taurine and magnesium and instead zeroing in on the key physiological problems that natural selection would have had to solve in order for acne to be naturally prevented; and then 4) discovering, amazingly, that the natural solutions to these key problems are taurine and magnesium.

Early on I figured that since sebum is the big problem in acne I should seek out information on sebum. Guessing that sebum inside sebaceous glands is a stream of little drops of lipids, I searched "lipid droplets" and found out there is a whole literature on the biology and life cycle of lipid droplets inside cells because almost all cell types of almost all multi-cellular organisms have lipid droplets to help with cellular energy storage and other functions. Sebaceous cells have simply used this lipid droplet system for an extra purpose—producing sebum. In particular, I sought to understand the beginning points and the end points of the life cycle of sebaceous lipid droplets.

The defining moments of the project were identifying the specific anti-acne mechanisms of action of taurine and magnesium in the sebaceous glands/ducts. One day in mid-April 2014 I sat back at my desk, staring at the computer, and asked "If I really want to understand how nature prevented acne in the natural ancestral environment, what specific mechanistic things would I most need to know?" Right away I realized that I would need to be able to answer 2 key technical questions, regarding the control of the life cycle of lipid droplets at their beginning and end:

- 1) How does nature periodically stop the sebaceous gland receptor LXR-alpha from activating the continued production of lipid droplets in the sebaceous glands, to prevent runaway oil production?
- 2) How does nature trigger protein kinase A phosphorylation of the sebaceous lipid droplet protein perilipin A to break down the large lipid droplets to micro-lipid droplets in a timely way, to prevent the clogging of the narrow sebaceous canals?

Immediately, though, I thought “But what could taurine and magnesium possibly have to do with these 2 fundamentally important events? Probably nothing . . . but I might as well do the Medline searches anyway, just to see.” Instantly with the first searches the key articles appeared on my computer screen: Taurine is an inhibitory ligand of LXR-alpha, halting lipogenesis, as discovered in liver cells (Hoang et al, 2012). Magnesium is the activator of protein kinase A phosphorylation (Adams, 2001; Yu et al, 2011)—and thus activator of perilipin A for the function of breaking down lipid droplets to micro-lipid droplets, discovered in adipose cells (A. Marcinkiewicz et al, 2006). With this seemingly stunning luck that such key experiments had been conducted in recent years, I felt that this taurine-magnesium path for acne was really worth pursuing. No one had ever linked these experiments to the subject of acne, so I would expand from there.

Humans in the Most Evolutionarily Natural Environments Do Not Experience Acne

The study by Loren Cordain et al (2002) showed an absence of acne among peoples with the most non-Westernized (“natural”) diets and ways of life. Specifically, among the Ache of Paraguay, hunter-gatherers recently transitioning to a more agricultural way of life, not a single case of active acne was found among all 115 individuals examined (although one man may have had acne scars). And on medical examination of the 1200 native Kitavans of the Trobriand Islands, Papua New Guinea, not a single acne lesion was found, even among the 300 subjects aged 15-25 years old. The emphatic conclusion of the Cordain et al study: acne is not natural to humans.

Although acne as a scourge and medical topic is historically ancient, having been written about by the ancient Egyptians, Greeks, and Romans (Tabasum et al, 2013; Mahmood and Shipman, 2017), in an evolutionary sense it is modern, in that it is almost surely a result of unforeseen consequences of living the post-hunter-gatherer (agricultural) way of life, which humans began doing roughly 10,000 years ago with the domestication of plants and animals. Acne is also not natural to animals. It is primarily a human problem, although various veterinary websites mention that acne can also occur in domestic cats, dogs, or horses. The formal medical literature has very little data on acne in animals, and it is not clear whether animal acne is exactly the same affliction (see, for example, Bedford and Young, 1981).

Insights Gleaned from the Comparative Dietary Studies Could Help Lead to Treatments for Acne or to Ways to Prevent It

If acne is not inherently part of being human, then perhaps it can be eradicated or prevented by understanding what went awry in post-hunter-gatherer societies to cause it. The dietary differences between ancestral hunter-gatherers and agricultural humans have been studied by S. Boyd Eaton and Melvin Konner (1985, 2010), with emphasis on the comparatively high quantity of meat and low glycemic load of ancestral hunter-gatherer diets, themes underlying some of their work with Marjorie Shostak (e.g. Eaton et al, 1996). The Cordain et al. study (2002) points to the comparatively high glycemic load of agricultural diets as one of the main likely culprits leading to hormonal changes that induce acne in westernized societies, discussed more fully in Part V. But the radical solution to the problem of agricultural diets causing acne—switching to a diet plan that imitates a Paleolithic hunter-gatherer diet (see Cordain (2005, 2006))—is achievable only for people who can stick to such a rigorous diet plan.

By contrast, if high-dose taurine with low-dose magnesium significantly protects against acne, then a simple solution to the problem of acne—supplementation with high-dose taurine with low-dose magnesium to help compensate for the chronically suboptimal amounts in agricultural diets—should be very easy for people to achieve.

Despite Being Not Natural to Humans, Acne is Difficult to Get Rid of, Is Still Not Generally Curable by Medicines, and Can Become Chronic

In current times acne is the most common skin disease (Zouboulis and Schagen, 2008). The worldwide prevalence of acne is estimated to be greater than 600 million persons per year (GBD, 2017). Although acne is mainly a teenage and young adult problem, it can continue to afflict people throughout adulthood (Collier et al, 2008); it can also afflict neonates and young children (Mancini et al, 2011; Eichenfield et al, 2013). Acne means un-wellness in many ways. It is characterized by papules, pustules, and various other types of lesions on the skin, primarily on the face, but often also on the neck, chest, or back. Often it leaves scars. Acne can greatly decrease quality-of-life (Cresce et al, 2014), and it can be psychologically devastating (Picardi et al, 2013). In addition, it can be physically uncomfortable in the sense that the afflicted person often feels the sensation of having lesions on the skin and may frequently pick at them, leading to worse lesions. Many dermatologists advocate aggressively treating acne, but current treatment options for any given patient are often ineffective or only partially effective or have dangerous, damaging, or other serious side effects. Even the newest anti-acne drugs in the pharmaceutical pipelines of recent years do not appear to be extremely effective against acne (Zouboulis et al, 2017). Acne is not considered to be a curable disease generally, other than curable by time, and for unlucky patients it can become chronic.

PART II: ACNE IN RELATION TO LIPID PRODUCTION

(Note: Many of the biochemical experiments cited in the technical parts of this paper, such as experiments related to lipid biosynthesis, used standard laboratory “immortalized” cell lines derived in the usual protocols from tumor cells. In interpreting results, it should be cautioned that lipid metabolic cell biology is not necessarily identical between normal cells and tumor cells of a given tissue type. Tumor cells often undergo forms of lipid metabolic reprogramming (Beloribi-Djefafia et al, 2016), including de novo lipogenesis (Li and Cheng, 2014), to favor their own propagation.)

Acne is a Disease of the Pilosebaceous Units

Acne is a skin disease of the pilosebaceous units (Zouboulis et al, 2008), the basic unit consisting of a sebaceous gland and two narrow pilosebaceous canals—a sebaceous duct and an attached hair follicle. Some pilosebaceous units have two or more separate sebaceous glands and ducts attached to the same hair follicle. The sebaceous glands, sebaceous ducts, and lower part of the hair follicles lie in the dermis of the skin, underneath the epidermis. Humans have numerous pilosebaceous units, in all skin regions of the body except the palms of the hand and soles of the feet (Smith and Thiboutot, 2008). The density of sebaceous glands in humans is about 400-900 per square cm in the head, and about 100 per square cm in other regions of the body (Montagna, 1963a). Sebaceous glands can be single-lobed or multi-lobed and are in continuous flux, with their outlines changing constantly (Montagna, 1963a).

Throughout an individual’s life, cells of the sebaceous glands differentiate and migrate from the periphery to the center of the glands, and as they migrate they begin synthesizing and accumulating lipids, eventually forming large formal lipid droplets (Schneider and Paus, 2010) that are surrounded by supporting structures of phospholipids and specialized proteins (Penno et al, 2013; Reue, 2011). After one to several weeks of differentiating, the mature cells of a sebaceous gland burst, in holocrine fashion, secreting their lipid contents through the sebaceous duct and into the hair follicle, which empties out the sebum onto the surface of the skin (Niemann, 2009; Smith and Thiboutot, 2008). In humans sebum is composed of triacylglycerols and diacylglycerols, squalene, wax esters, cholesterol esters, and free fatty acids (Camera et al, 2010). The components of sebum, which are dermal lipids, are mostly different from epidermal lipids (Picardo et al, 2009; Pappas, 2009), which are not thought to play a significant part in acne.

The function of sebum in humans is not fully known yet (Smith and Thiboutot, 2008), but sebum is a lubricant (Pappas et al, 2009) that may form a waterproofing barrier for the skin (Smith and Thiboutot, 2008), also preventing desiccation. In non-human mammals, as commonly pointed out by naturalists, sebum waterproofs the fur. Waterproofing fur is likely to be the primary evolved function of sebum in mammals, discussed further below, although the degree of waterproofing would be

expected to vary considerably among the different species of wild mammals, depending on their typical exposure to rain, snow, and water from oceans, lakes, and rivers.

Acne occurs if sebum clogs a sebaceous duct and/or its hair follicle. Sebum level and severity of acne are correlated (Choi et al, 2011). Sebum differences among humans may account for much of the degree of clogging. In a sebum analysis of individuals with and without acne (Pappas et al, 2009), acne patients produced 59% more sebum, and they produced much more squalene. Squalene was up-regulated 2.2-fold in acne patients compared to non-acne controls. There are some ethnic differences in the constituents of sebum and other skin characteristics that may lead to some of the acne variation among the population (Rawlings, 2006). There are also gender differences in skin that influence acne (Dao and Kazin, 2007).

Constituents of sebum differ slightly from species to species (Stewart, 1986). Pilosebaceous units are structures in the skin of most mammals, but non-human mammals are much less susceptible to acne than humans are. In mice experiments, genetically altered sebum has been shown to block the hair canals (Maier et al, 2011). But even though some degree of clogging of the pilosebaceous units can be induced in some lab animals, and there are sporadic cases of acne or acne-like eruptions among domestic pets, there are no known good animal models for acne.

The reason why humans are much more prone to acne than are other mammals may be that sebaceous glands and ducts are more important tissues in the furry mammals than they are in humans; so these structures in non-human mammals get better maintenance and safeguards against dysfunction than do these structures in humans. Atrophic sebaceous glands in genetically altered mice lead to impaired water repulsion and defective thermoregulation after water immersion (Chen et al, 2002). This experimental result implies that in natural environments, inadequate sebum production could lead to serious hypothermia during rainfall or swimming, if water is not repelled from the fur. Since humans do not have fur, they do not face the same dangers from getting wet. Therefore their pilosebaceous units do not appear to be as critical for survival and so do not get the same degree of anti-clogging protection. Although humans almost surely have the same basic anti-acne mechanisms (discussed in Part III) as do the non-human mammals that have sebaceous glands, humans may get less vigilance with regard to the continuous smooth operation of these mechanisms when normal biochemical profiles are altered through drastic dietary changes.

The sebaceous glands are stimulated by androgens to grow larger and to increase lipogenesis (Pelletier and Ren, 2004). Different regions of human skin show differences in sebum production corresponding to regional fluctuations in androgen susceptibility (Seo et al, 2014). Androgen production also varies according to stage of life. In humans androgen-dependent sebum secretion typically is high in neonates, falls soon thereafter, remains low during early childhood, and rises again during puberty, to a maximum in young adults (Zouboulis and Boschakow, 2001).

Sebum levels usually decrease after menopause in females, but not until the eighth decade in males (Zouboulis and Boschakow, 2001). Androgens stimulate sebum synthesis in part through activation of the SREBP (sterol regulatory element binding protein) pathways (Rosignoli et al, 2003), which are discussed in Part III.

Because androgen production increases sharply during the teenage years, acne usually begins then. Since there are many androgen receptors in the sebaceous glands, the body is apparently designed to produce sebum in response to signals that the teenage years have begun. Why this should be so is a mystery, but since androgens often lead to enhanced aggression (Berenbaum and Resnick, 1997), which may mean the increased risk of wounds to the skin, such as scratches from fighting, it is possible that the excess oily/waxy sebum is produced at puberty to make the skin more pliable and resistant to tear. This speculation on the sebum-androgen relationship is brought up here because probably all dermatologists wonder why the mechanism of sebum production is designed to increase sebum output at puberty—a mechanism that has wreaked havoc on the human face.

Comparative Mammalian Data Shows the Importance of Sebaceous Glands

Comparative wild mammalian data sheds light on why good animal models for acne are unlikely to be found despite the fact that most mammalian species have the same basic sebaceous structures as humans. It turns out that humans are exceptions to the general anatomical mammalian pattern that emerges when the skin of the different species of mammal is surveyed with regard to the presence or absence of sebaceous glands: the trait of numerous sebaceous glands distributed throughout most dermal regions of the body is very highly correlated with the trait of furriness. Of the sparsely-haired or hairless mammalian species, humans appear to be the only ones with numerous or wide distribution of sebaceous glands.

Although the evidence presented in this subsection may seem like a slight detour from the main focus of the paper, it helps in the overall understanding of sebaceous function and dysfunction. (Note on definitions and assessments of the comparative mammalian data: By mammalian species are meant natural wild mammalian species, not artificially-bred laboratory, domestic pet, or farm mutants/breeds. By sebaceous glands are meant the standard sebaceous glands that produce sebum, not the specialized free-floating scent-marking glands, other scent glands, or Meibomian eyelid glands that were modified from sebaceous glands through evolution to serve a very different purpose from that of waterproofing fur. A researcher investigating accounts of sebaceous glands among mammals should be aware that some of the secondary sources misreport the data that originated from primary sources. Also, a researcher should be aware that for an accurate assessment of sebaceous gland distribution, skin samples from many different regions of the body need to have been assessed; for example, taking together the different studies of rhino skin and hair, it is found that although a scattering of sebaceous glands is present in skin of the nape, no sebaceous glands are present in skin of the cheek, shoulder, abdomen, flank, or rump.)

Whether terrestrial or aquatic species, the non-human mammals that are non-furry lack sebaceous glands in every or almost every dermal region of the body: see, for example, elephants (Spearman, 1970; Smith, 1890; Eales, 1925; Walter, 2010); rhinos (Plochocki et al, 2017; Cave, 1969; hippos (Luck and Wright, 1964); whales and dolphins (Montagna, 1963b; Sokolov, 1982, p. 607); sea cows (Reep et al, 2002). Among furry mammalian species, by contrast, it appears that all have ample and wide dermal distribution of sebaceous glands. Even the furred lesser anteater—reported initially from inspection of one specimen to lack sebaceous glands (Machida et al, 1966)—turns out actually to have numerous sebaceous glands, that look, however, somewhat different from usual, as they are relatively small, single-lobed, and each pressed up against its corresponding hair follicle rather than flared out (see Sokolov, 1982, p. 172). The general mammalian pattern of sebaceous glands correlating with furriness is so marked that although elephants, which have only scattered hairs and so are not furry, lack sebaceous glands, the closely-related but furry woolly mammoths (now extinct) had ample sebaceous glands, as evidenced from mammoth skins preserved in Arctic permafrost (see Repin et al, 2004).

This general pattern would not be surprising if sebaceous glands and hair follicles were by necessity paired together. But sebaceous gland distribution does not have to track hair follicle distribution. Sebum-producing sebaceous glands in mammals can be free-floating, i.e. not connected to hair follicles. In fact, in lemurs, most sebaceous glands open directly onto the surface of the skin instead of into the pilary canal of a hair follicle (Montagna, 1962; 1963b). Inversely, hair follicles can exist without sebaceous glands attached to them; for example, the widely spaced-apart hair follicles of elephants do not have associated sebaceous glands. Nonetheless, from the comparative mammalian data, it is obvious that sebaceous glands serve an important purpose in furry mammals but are not needed in non-human non-furry mammals.

In humans, a link between sebaceous glands and need for skin protection against aggression seems to be supported at least indirectly by comparative mammalian anatomy: the non-human sparsely-haired or hairless natural mammals, all of which appear to lack sebaceous glands, have thick tough skin or else blubber as partial protection against aggression. Blubber, though, does not negate the need for sebaceous glands if the animal has fur; all pinnipeds, for example, are furred and have sebaceous glands, including the seals (Sokolov, 1982) and short-furred walruses (Luck and Wright, 1964), which have thick layers of blubber.

One seemingly near-exception to the observation that non-human hairless mammals lacking sebaceous glands have thick skin for defense against aggression is the naked mole-rat, a mammal in a category of its own in many ways. This strange mammal—subterranean, long-lived, poikilothermic (cold-blooded), eusocial (living in colonies like bees and ants, with a reproductive queen and many drones whose puberty is suppressed)—is basically hairless, having only scattered tactile hairs, and

it lacks sebaceous glands. Although its skin is not thick, it is significantly thicker than in its furry counterpart, the subterranean common mole-rat, which does have sebaceous glands (Daly and Buffenstein, 1998). Apparently for naked mole-rats the danger from irregular spikes in aggression during their life cycles is not sufficient to justify the thermoregulatory costs of even thicker skin. Given its special circumstances, the naked mole rat too fits the general mammalian pattern.

In humans, sebaceous activity to a large extent tracks androgen production, probably for defensive reasons; in furry mammals, however, the extent to which sebum production needs to be androgen-linked is unclear, if the main function of their sebum is to waterproof fur. Androgen production appears to trigger the widening of hair diameters of the fur of mammals (Davis et al, 2010), which likely increases the surface area of the fur that needs to be coated with sebum. But the numbers and lengths of hairs change more noticeably according to the geological seasons rather than the androgen-linked aggression-linked mating seasons. So total sebum production in non-human mammals is likely to fluctuate according to a somewhat different set of cues than it does in humans.

In the mammalian species most closely related to humans—the chimpanzees and gorillas—a kind of transition to the human sebaceous situation can be observed. The skin of the faces of these apes has hairs but is not furry, yet has many sebaceous glands (Sokolov, 1982); although their facial skin is thicker than their skin of most other areas of the body (Sokolov, 1982), it is not thick compared to the skin of mammals lacking sebaceous glands. Chimpanzees and gorillas exhibit high intra-species aggression in which the face is used for biting, and therefore the thicker facial skin probably makes sense for protection, compensating for the lack of fur in that area. The retention of sebaceous glands in ape faces may have been the prelude to the retention of sebaceous glands throughout the non-furry skin of hominids in the evolutionary transition to modern humans.

In sum, humans appear to be the only mammals that are non-furry yet have numerous sebaceous glands. They may also be the only non-furry mammals with relatively thin skin and no blubber and therefore in need of sebaceous glands for help with skin defense (e.g., better resilience and resistance to tear). Humans appear to be the only mammals that do not conform to the general mammalian pattern regarding sebaceous glands, and they are also the only mammals known to be easily susceptible to acne when deviating from the diets most natural to their species. In humans, sebaceous glands are important enough to have persisted yet are unlikely to be critical. Because the anti-acne mechanisms in pilosebaceous units seem to function more strongly in non-human mammals than in modern agricultural humans, the lab animal research that helps reveal these mechanisms can be useful in finding clues to preventing dysfunction of these mechanisms in humans. The goal in this research paper is to explore how to keep the anti-clogging mechanisms of the sebaceous structures of modern agricultural humans functioning as smoothly as in the furry mammals, or as in the humans of evolutionarily natural environments.

Excess Sebum Production Can Affect Other Factors that Influence Degree of Acne

Many dermatological studies point out that the androgen-driven clogging by sebum is often exacerbated by at least 3 other factors: hyperkeratinization and excess shedding of cells in the hair follicles, leading to excess debris in the sebum; infection of clogged areas by *Propionibacterium acnes*; and inflammation (Dawson and Dellavalle, 2013; Smith and Thiboutot, 2008). If lipogenesis were kept at a much lower level, these secondary factors would be much less likely to occur.

Understanding Lipid Droplet Biology May Be Key to Understanding Acne

In order to understand acne, it is important to study lipid droplets, which in sebocytes contain the sebum. There are many studies on lipid droplet biology and formation in cells (e.g., Thiele and Spandl, 2008; Thiam et al, 2013; Guo et al, 2009; Pol et al, 2014; Walther and Farese, 2009; Reue, 2011) and some studies of lipid droplet lipolysis, fragmentation and dispersion (e.g., Paar et al, 2012; Ducharme and Bickel, 2008; A. Marcinkiewicz et al, 2006). Most of the studies on lipid droplet biology are on non-sebaceous cells, especially adipocytes, but some are on sebocytes (Dahlhoff et al, 2013). Lipid droplets are formed in virtually all cells of the body, from the endoplasmic reticulum, as a compact way for cells to store energy as lipids and to provide building materials for local membrane synthesis and repair (Brasaemle, 2007).

Lipid droplets are especially numerous in sebocytes. But their apparent primary function in sebocytes—storage of sebum—is different from their primary function in other cells. Furthermore, the composition of lipids from sebocyte lipid droplets is different from that of adipocyte lipid droplets (Dahlhoff et al, 2013), an indication that there may be other differences between lipid droplets in sebaceous glands versus other tissues. Diversity of lipid droplets in different cell types and lipid droplet stages is further discussed in Thiam and Beller (2017).

Lipid droplet formation in all cells entails the packaging of lipids into organelles whose surfaces are comprised of a layer of phospholipids interspersed with various types of regulatory proteins, which include the perilipins (Reue, 2011; Walther and Farese, 2009). The different perilipins (also referred to as PLIN proteins) have different functions. Perilipin A (PLIN1a), for example, has the function of eventually breaking down the lipid droplets to micro-lipid droplets (A. Marcinkiewicz et al, 2006). This step is necessary in cells expressing perilipin A because cells manufacture lipid droplets that are initially large, for favorable surface area to volume ratio, as an efficient way to store lipids for later utilization. Lipid droplets have been observed in a wide range of different sizes even within the same cell (Paar et al, 2012). In most cell types they become very round (Penno et al, 2013). They are also very mobile inside cells, where they may ride on microtubules like tracks (Martin and Parton, 2006).

The physical course travelled by sebaceous lipid droplets in their journey through the pilosebaceous structures, in relation to the particular life stage and size of the lipid droplets, is likely to be an important factor in whether the lipid droplets contribute to acne. Sebum is discharged to the skin surface via the sebaceous duct (Latham et al, 1989) and the hair follicle, after the sebocytes burst and release their lipid droplets. The exact area in the pilosebaceous unit where the clogging by sebum likely occurs is the sebaceous duct and the part of the hair follicle near it. It is not yet clear, however, at what point along the path from the sebaceous gland through the sebaceous duct and hair follicle that the lipid droplets break down to micro-lipid droplets, and that all the droplets dissolve their boundaries and become simply sebum. In early electron microscopic observations of the human sebaceous gland, Charles (1960) found that lipid droplets were squeezed up the sebaceous duct, and that the duct contained compressed secretory droplets that appeared to retain their identity.

The sebum/lipid droplets appear to be the main culprit in acne. Large lipid droplet size in the pilosebaceous units is not conducive to smooth transport of numerous lipid droplets through narrow sebaceous canals. The occurrence of acne means that something in the dermal system went awry that allowed the clogging of sebaceous ducts and/or hair follicles by sebum—such as the production of lipid droplets that were too numerous or too large, or a delay in the breakdown of lipid droplets, or the production of sebum that was less fluid than optimal. Augmented or accelerated lipogenesis could probably cause lipid droplets to form that are too numerous or too large. An inability of perilipin A to break down the lipid droplets rapidly enough might lead to clogging of the sebaceous ducts and/or hair follicles.

PART III: HOW TAURINE WITH MAGNESIUM MAY NATURALLY PREVENT ACNE

The natural design of the pilosebaceous units includes the use of taurine and magnesium in ways that help prevent clogging by sebum.

Two fundamental problems that natural selection had to solve in order to enable sebum to be produced deep inside the skin and transported to the exterior of the skin without causing clogging (acne) are: 1) how to halt sebaceous lipogenesis frequently enough to prevent runaway lipid production; and 2) how to break down the large lipid droplets to micro-lipid droplets in a timely way to prevent blockage of the narrow sebaceous ducts and hair follicles. This part of the paper will show how taurine and magnesium are the natural molecular triggers of the physiological mechanisms that solve these 2 problems.

Some dietary molecules as well as some molecules naturally synthesized in the body are able to activate or inactivate specific sequences of physiological events by interacting with target proteins in the body via methods that alter the conformations of the target proteins. Two such methods are: 1) binding as ligands to receptor proteins, either as agonists, antagonists, partial agonists/antagonists, or

inverse agonists; and 2) catalyzing protein kinase phosphorylation, the enzymatic attachment of phosphate groups to proteins. Taurine and magnesium in the pilosebaceous units appear to trigger anti-acne mechanisms via these two methods.

Taurine Very Likely Limits Sebaceous Lipogenesis

The pilosebaceous units take up extra taurine apparently for the special function of keeping sebaceous lipogenesis in check.

The Pilosebaceous Units Take Up Taurine

Animal experiments on the distribution of taurine in tissues show taurine to be expressly taken up by the pilosebaceous units, indicating some important function for taurine there. In rat neonates, within an hour after intraperitoneal injection, ³⁵S-taurine is accumulated in the sebaceous glands at among the highest density of all tissues in the body (Shimada et al, 1984). In adult mice, after injection of [1,2-³H]taurine, a very high density of free form taurine was found in the outer root sheaths near the opening of the hair follicles, and high taurine accumulation occurred in the peripheral part of the sebaceous glands as well as in the outer root sheaths just below the insertion of the sebaceous glands (Watanabe et al, 1995). Ample taurine availability in the body, at least in these animals, leads to concentrated taurine levels in the pilosebaceous units.

When taurine is not necessarily ample, it is still found in the pilosebaceous units in animals, although probably at lower density. In an immunochemical study in adult dogs and rats on the content and distribution of taurine in squamous epithelia, sebaceous cells were immunolabelled, but usually less intensely so than other cell types in the dermis; the taurine immunostaining was variable between individual cells, both in nuclei and cytoplasm (Lobo et al, 2001).

In humans, in samples of breast skin, taurine was found to be naturally present in all levels of the dermis, and upon topical application of taurine in solution, the content of taurine in each level of dermis was significantly increased within an hour (Da Silva et al, 2008); it was not specified in this study whether taurine was found specifically in the pilosebaceous units. It is not yet known in humans whether high (therapeutic) oral or topical doses of taurine, taken over an extended period of time, would cause taurine to be accumulated at high density in the pilosebaceous units, but given the above studies, this scenario seems likely. In the context of the injection studies in mice and rats, a main question to pursue is why taurine is taken up at such high density by areas of the pilosebaceous unit after dosing. What special function does taurine perform there, if any, other than its usual role as an osmolyte of cells? It is likely that taurine uptake in the pilosebaceous units of humans and animals helps prevent the clogging that leads to acne.

Taurine is a Natural Inhibitory Ligand of the Lipogenic Nuclear Receptor LXR-alpha

The main way that taurine seems to naturally help prevent acne and limit its severity is by limiting the amount of lipogenesis in the sebaceous glands. Taurine likely accomplishes this function by binding as a lipogenesis-inhibiting ligand to the major receptor in the sebaceous glands known to induce lipogenesis, the nuclear receptor LXR-alpha (liver X receptor-alpha).

Like certain other nuclear receptors, the LXR-alpha is a ligand-activated transcription factor that forms a heterodimer with the RXR (retinoic X receptor) when activated by an appropriate ligand; the heterodimer then binds to specific gene sequences of DNA. The main known way that the LXR-alpha induces lipogenesis in a cell is by binding to a ligand of the type oxysterol, which changes the conformation of the LXR-alpha in ways that make it bind, with RXR, to DNA sequences that induce the expression of sterol regulatory element-binding protein (SREBP) transcription factors. SREBP activation induces lipid synthesis in the endoplasmic reticulum, resulting in lipid-filled lipid droplets budding off the endoplasmic reticulum to various parts of the cell cytoplasm. The number of LXR-alpha per cell probably fluctuates considerably in response to specific cellular signals, influencing the level of lipogenesis.

Although the biochemistry of the LXR-alpha is usually studied in hepatocytes or adipocytes, because these are the well-known lipid-metabolizing areas of the body, the LXR-alpha is also present in certain other kinds of cells, including sebocytes. (Whereas the LXR isoform LXR-beta is expressed in almost all mammalian tissues, the isoform LXR-alpha is expressed only in a subset of tissues.) Studies by Russell et al (2007) and Hong et al (2008) show that LXR-alpha is expressed in human sebocytes (SZ95 cell line), and that LXR-alpha in sebocytes typically stimulates sebaceous lipid synthesis.

In sebum production there are 2 SREBP-driven biochemical pathways of lipid synthesis: 1) the fatty acid/triacylglyceride synthesis pathway activated mainly via SREBP-1c, or sometimes SREBP-1a; and the squalene/cholesterol synthesis pathway, activated mainly via SREBP-2, or sometimes SREBP-1a. The wax esters in sebum (Downing et al, 1977) are also synthesized via the fatty acid pathway, as they are formed from some of the fatty acids that are then joined with fatty alcohols via wax synthase (Pappas et al, 2002), which sebaceous lipid droplets obtain either from the ER or from contact with peroxisomes (Cheng and Russell, 2004a, 2004b; Gao and Goodman, 2015). LXR-alpha directly initiates the SREBP-1c pathway of fatty acid/triacylglyceride biosynthesis (Xiao and Song, 2013), increasing the lipid level of the cell. There is some evidence also that the 2 SREBP-driven biochemical pathways of lipid synthesis are coupled in terms of their relationship to LXR-alpha, as discussed further on.

Because synthetically-developed agonists to LXR-alpha have been shown to increase lipogenesis in sebocytes in vitro, Hong et al (2008) point out that developing selective antagonists to LXR-alpha might provide a therapeutic class of new anti-acne agents. The connection between LXR-alpha and acne was further measured by

Nada (2012), who quantitated and compared LXR-alpha RNA levels in back skin biopsies from inflammatory lesions of acne patients, comedonal lesions of acne patients, and normal skin of healthy controls. Results showed that acne lesions express significantly more LXR-alpha RNA. In particular, the inflammatory acne lesions had almost double the normal level of LXR-alpha RNA, although this correlation was not otherwise influenced by the severity, duration, or course of the patient's acne. The author of this study, too, emphasizes that LXR-alpha could be an important therapeutic target for the treatment of acne.

The relevant question regarding acne, therefore, is where to look for biochemical ways to suppress LXR-alpha activity. In order to maintain stability of functionality, biological systems generally have regulatory negative feedback loops, such that certain pathway byproducts or end products serve as endogenous inhibitory ligands of the receptors to prevent overactivity. Additionally, cells might maintain a pool of other natural inhibitory ligands that function to balance the regulatory system to prevent major dysregulation.

According to Hoang et al (2012), who studied the LXR-alpha in the context of lipid regulation in the liver, the ligand-binding pocket of the LXR-alpha can accept an array of different ligands of different shapes, structure and volume.

Finding the natural ligand that is the best molecular fit to the sebaceous LXR-alpha for the purpose of inhibition of lipogenesis would provide a therapeutic way to biochemically amplify natural mechanisms of suppression of sebum production.

Taurine is a natural LXR-alpha ligand that appears to halt lipogenesis rather than stimulate it. In a key in vitro study of human liver cells (HepG2 cell line) by Hoang et al (2012), taurine was shown to be a ligand of LXR-alpha that inhibited lipogenesis, resulting in a dose-dependent marked reduction in cellular lipid levels. Taurine as a ligand of LXR-alpha induced levels of Insig-2 (insulin induced gene 2), which delayed nuclear translocation of SREBP-1c, the activator of the fatty acid/triacylglycerol pathway. The increase in either Insig-1 or Insig-2 is an important inhibitory step in lipid synthesis, because the Insigs block the transfer of the SREBPs from the endoplasmic reticulum to the Golgi apparatus, preventing the SREBPs from entering the nucleus to initiate steps for lipid synthesis (Sun et al, 2005; Yabe et al, 2002). Meanwhile taurine activated transcription of various other genes involved in usual LXR-alpha functions, such as reverse cholesterol transport, the efflux of excess cholesterol from cells. Huang (2014) too, in a study on natural modulators of LXR, points out that the study by Hoang et al (2012) suggests that taurine is a direct LXR-alpha antagonist.

This lipid-suppressive action of taurine may be one of the keys to understanding natural acne prevention. Although the study of taurine as an inhibitory ligand was performed on the LXR-alpha of liver cells, it seems extremely likely that taurine would have the same effect on the LXR-alpha of sebaceous cells. If taurine generally has such an inhibitory effect on LXR-alpha, then taurine in the sebaceous glands

would limit sebaceous lipogenesis, helping to reduce or prevent acne. Since taurine is an endogenous molecule, its suppressive action on the LXR-alpha very likely represents one of its natural functions.

The possible additional effects of taurine as ligand of LXR-alpha on SREBP-2, SREBP-1a, and Insig-1 were not specifically measured in the Hoang et al study, but such relationships could be investigated in future experiments. There is at least indirect evidence that an LXR-alpha antagonist, such as taurine, would also have a suppressive effect on the SREBP-2 squalene/cholesterol pathway, because LXR-alpha agonists have an activating effect on the SREBP-2 pathway, and a strong LXR-alpha antagonist could block an LXR-alpha agonist from binding to the LXR-alpha and activating it. Examples of synthetic LXR-alpha/LXR-beta agonists activating SREBP-2 in human cells are the following (as pointed out by He et al [2014]): in astrocytes they upregulate SREBP-2 expression (Abildayeva et al, 2006); and in HepG2 cells they greatly increase cholesterol synthesis (Aravindhham et al, 2006), which is SREBP-2-driven. Notably for acne, this latter study implies that LXR-alpha activation by agonists increases squalene synthesis, since squalene is a step to cholesterol. Reciprocally, activation of the SREBP-1c-activated pathway of fatty acid/triacylglyceride synthesis depends on the SREBP-2 pathway to generate cholesterol-derived agonist ligands for LXR (Rong et al, 2017). Since virtually all cells have the mechanisms for cholesterol efflux by reverse cholesterol transport (Schofield, 2017), if taurine in sebaceous cells suppresses new cholesterol synthesis while activating reverse cholesterol transport, then it also helps deprive LXR-alpha of agonist ligands for fatty acid/triacylglyceride synthesis.

Taurine thus is likely to be part of the regulatory system that keeps sebaceous lipogenesis in check. Amplifying the taurine-LXR-alpha interaction by augmenting taurine levels in the pilosebaceous units through oral or topical supplementation may be therapeutic against acne.

Taurine May Also Be an Inhibitory LXR-alpha Ligand in the Adrenal Cortex, Limiting Acne-Causing Androgen Production

Taurine and LXR-alpha are also both present at significant levels in adrenal glands, glands that produce some of the androgens that can cause acne. For example, the adrenal glands in cats have been shown to have high concentrations of taurine, and the accumulation of [35S]taurine by the adrenal glands is rapid and high, almost the highest of all tissues (Sturman et al, 1977); and the adrenal glands of neonatal and adult rats accumulate [35S]taurine at high concentrations (Shimada et al, 1984). LXR-alpha is expressed by the adrenal glands (shown in mice) (Cummins et al, 2006), where it helps regulate adrenal steroidogenesis (Nilsson et al, 2007). Androgen production in the adrenal glands occurs via lipogenesis, when lipid droplets in the adrenal cells accumulate cholesterol to be transferred to mitochondria for synthesis of pregnenolone (Chanderbhan et al, 1981; Boyd et al, 1983), the precursor to steroids such as androgens. If taurine is an inhibitory ligand of adrenal LXR-alpha, as it is of liver LXR-alpha, then taurine might limit

adrenal lipogenesis, and thereby help prevent excess androgen production and decrease severity of acne. Clinically, sebum production has been shown to greatly decrease in patients who undergo bilateral adrenalectomy, a result attributed to the depletion of adrenal androgens (post-operative glucocorticoid levels were maintained medically) (Pochi and Strauss, 1977). The connection between taurine and LXR-alpha may turn out to be extremely important in the natural and clinical control of acne.

Taurine Also May Be a Ligand of Nuclear Receptor PPAR-gamma

Computer simulations show that the structure of taurine can be flexibly docked into the ligand-binding site of the PPAR-gamma (peroxisome proliferator activated receptor-gamma), supporting biological experiments showing a likely ligand-receptor relationship between the two (Song et al, 2011). PPAR-gamma helps regulate lipid synthesis, but in ways not yet fully clear and consistent. PPAR-gamma is expressed in many tissues of the body, including those of the pilosebaceous units, such as the sebaceous glands, sebaceous ducts, and hair follicles (Trivedi et al, 2006). PPAR-gamma is also expressed in the adrenal glands (Liu et al, 2010; Mannelli et al, 2010). The specific ligand-docking experiment by Song et al (2011) used human retinal pigment epithelial cells, showing that taurine down-regulated the pathway of PPAR-gamma-dependent pro-inflammatory mediators. This particular result suggests, incidentally, that taurine might also be able to curtail some of the inflammation of acne.

The effect of taurine on PPAR-gamma-related lipogenesis, however, was not tested in the Song et al experiment. Downie et al (2004) showed that some PPAR-gamma ligands inhibit sebaceous lipogenesis in human whole organ sebaceous gland cultures, but taurine was not one of the ligands tested. Mastrofrancesco et al (2017), using the SZ95 line of human sebocytes, also showed that PPAR-gamma modulation can regulate sebogenesis and inflammation, and they further pointed out that synthetic modulators of PPAR-gamma could potentially represent therapeutic strategies for acne treatment.

It seems plausible that taurine as a natural PPAR-gamma ligand might function as an antagonist, to inhibit PPAR-gamma-related lipogenesis, since taurine as an LXR-alpha ligand appears to function to inhibit LXR-alpha-induced lipogenesis; but further experiments are needed regarding the relationship between taurine and PPAR-gamma. Supporting the idea that one of functions of taurine is to help keep lipogenesis in check is a study in pre-adipocytes by Deng et al (2015) showing that one of the enzymes involved in the pathway of internal taurine synthesis from cysteine—cysteine dioxygenase 1 (CDO1)—interacts with PPAR-gamma in such a way that taurine synthesis is facilitated when lipid droplets are forming.

In sum, taurine may be a natural inhibitory ligand of the nuclear receptors—especially LXR-alpha—that affect acne, suppressing the actions that increase lipogenesis, while maintaining certain other LXR-alpha functions. Understanding

taurine's role as a natural ligand for LXR-alpha should help in understanding the natural prevention of acne.

Magnesium Very Likely Catalyzes the Breakdown of Sebaceous Lipid Droplets to Micro-Lipid Droplets

Lipid Droplets Should Be Small When Entering the Narrow Pilosebaceous Canals

Excessive lipid droplet size in the sebaceous ducts or the hair follicles could very likely clog these narrow pilosebaceous canals. It is still not clear exactly where along the sebum path—from the sebaceous gland, through the sebaceous duct, through the follicular canal, to the surface of the skin—the numerous sebaceous lipid droplets are supposed to break down to micro-lipid droplets, and the micro-lipid droplets to usable lipid constituents. As mentioned above, early electron microscope images show lipid droplets of some size being squeezed up the sebaceous ducts (Charles, 1960). Whether this squeezing depicts an unnaturally tight space for lipid droplets along their journey or a naturally normal scenario has not been investigated yet. Data do not appear to be available on whether intact sebaceous lipid droplets reach the hair follicles from the sebaceous ducts.

The diameters that are important for assessing whether the sizes of sebaceous lipid droplets are factors in acne are those of the lipid droplets, the micro-lipid droplets, the sebaceous ducts, the hair follicles, and the hair shaft in the hair follicles. Lipid droplets in most cells come in a range of sizes. The diameters of lipid droplets (in cells other than adipocytes, which produce extremely large lipid droplets) are usually less than 1 micrometer, and they rarely, but sometimes, exceed 10 micrometers (Suzuki et al, 2011). The diameters of the smallest detectable lipid droplets, by contrast, are only 70 nanometers (Suzuki et al, 2011). (The Suzuki study did not specify whether these small lipid droplets signified micro-lipid droplets resulting from the breakdown of larger lipid droplets.) Measurements of the diameters of the sebaceous ducts and of the hair follicles in the region near the ducts do not seem to be available in published studies, but in the histological images available online the diameters of both appear to be narrow relative to the diameters that would be required for the smooth conveyance of clusters of large lipid droplets. The diameter of the opening of the hair follicle to the exterior skin of the forehead, a common acne area, can be calculated from a study by Cunliffe et al (1976) to be about 50 micrometers; and that opening needs to be large enough to contain the hair shaft, which in the forehead has a diameter of about 18 micrometers (Otberg et al, 2003), as well as to enable the flow of sebum and cellular debris surrounding the hair. The diameters of the narrowest parts of the sebaceous ducts and hair follicles are probably less than the 50-micrometer diameter of the opening to the exterior skin.

If sebaceous lipid droplets are not broken down into micro-lipid droplets or smaller constituents before or while they are squeezed through the narrow pilosebaceous canals, then clusters of large lipid droplets could likely clog these areas. Of note is

that squalene accumulation is associated with the clustering of lipid droplets—defined as the aggregation of 6 or more lipid droplets—as shown by Ta et al (2012) in yeast cells and in mammalian adipocyte and ovary cell lines. (Lipid droplet experiments in yeast are often significant for humans as well because lipid droplet biochemistry is highly conserved throughout the evolution of organisms, from yeast to mammals.) Ta et al (2012) showed in their yeast experiment that the effect of squalene on clustering is so pronounced that reducing the level of squalene restores the lipid droplet distribution to normal. As discussed above, squalene is present in much greater quantities in the sebum of people with acne than without acne. Thus, people whose sebaceous glands produce greater than average amounts of squalene are at risk for sebaceous lipid droplet clustering and are especially in need of the mechanisms for breaking down lipid droplets to micro-lipid droplets and dispersing them. Otherwise, the diameter of a cluster of large lipid droplets could exceed the diameter of the sebaceous ducts and hair follicles of the pilosebaceous units, clogging them.

Magnesium Triggers Protein Kinase A Phosphorylation of the Lipid Droplet Surface Protein Perilipin A (PLIN1a), Which Breaks Down Lipid Droplets to Micro-Lipid Droplets

Lipid droplets are coated with several types of perilipin proteins, which perform various functions involving stabilizing the lipid droplets and controlling lipolysis of them (Brasaemle, 2007). Perilipin A, also known in more recent nomenclature as PLIN1a, may be integral to acne prevention.

In a key in vitro study in murine adipocytes (3T3-L1 cell line), A. Marcinkiewicz et al (2006) found that protein kinase A (PKA) phosphorylation of perilipin A drives the fairly rapid fragmentation and dispersion of lipid droplets. This phosphorylation causes the lipid droplets to break down into myriad dispersed micro-lipid droplets.

Perilipin A is also expressed on the surface of lipid droplets in sebocytes, as demonstrated both in hamster sebocytes (Akimoto et al, 2005) and in human differentiated SZ95 sebocytes (Dahlhoff et al, 2013). In earlier studies, perilipin A was shown to be associated with adipose cells as well as steroidogenic cells, such as in adrenal cortex (Servetnick et al, 1995). Of note is that Thiboutot et al (2003) found that sebaceous cells are steroidogenic cells. Adipocytes have also been found to be steroidogenic cells (Li et al, 2014). It is highly likely that perilipin A performs the same regulatory function on lipid droplets of sebocytes as of adipocytes, fragmenting and dispersing the lipid droplets upon PKA phosphorylation.

Magnesium plays a critical role in protein kinase phosphorylation, including PKA phosphorylation (Yu et al, 2011). Magnesium is even considered to be the physiological activator of the protein kinases, enzymes with specialized catalytic binding sites for magnesium (Adams, 2001). At the catalytic site cleft of the PKA molecule, either 1 or 2 magnesium ions bind, in addition to ATP (adenosine triphosphate), slightly altering the contour of the cleft; then a substrate protein,

such as perilipin A, binds along this cleft, and a phosphate is transferred from ATP to the substrate protein (Ubersax and Ferrell, 2007; McClendon et al, 2014). Magnesium at the catalytic site functions in part to help stabilize the orientation of the phosphate being transferred from ATP to the substrate protein (Wang and Cole, 2014), which results in a conformational change to that substrate protein. This phosphate-transfer role is crucial, as phosphates drive many biochemical transformations in nature (Westheimer, 1987; Hunter, 2012). The dynamics of PKA that occur when magnesium ions bind at the catalytic site are visualized in McClendon et al (2014).

Magnesium is also required at an earlier stage of the PKA phosphorylation cascade: PKA functionality is dependant on cyclic-AMP (adenosine monophosphate), which requires the conversion of an ATP molecule to cAMP via the enzyme adenylyl cyclase; and this latter enzyme requires 2 magnesium ions for activation (Zimmermann et al, 1998).

Therefore, since the activation of perilipin A requires magnesium-catalyzed PKA phosphorylation, sufficient magnesium in the pilosebaceous units is required for the natural prevention of acne if the perilipin A on sebaceous lipid droplets is to perform the function of breaking down the lipid droplets to micro-lipid droplets. The result of adequate magnesium should be more fluid flow of sebaceous lipid droplets, with less chance of clogging.

(Note: The above-mentioned Dahlhoff et al (2013) human sebaceous cell line SZ95 study and Akimoto et al (2005) hamster sebaceous cell line study emphasize that the expression of perilipin A (PLIN1a) increases dramatically with sebaceous cell differentiation, whereas it is low in undifferentiated sebaceous cells. These results make sense, because perilipin A in sebaceous cells would be expected to be upregulated close to the stage of holocrine burst, when lipid droplets need to be broken down before or upon entering the narrow pilosebaceous canals. The perilipins PLIN2 and PLIN3, in contrast to PLIN1a, have functions that promote lipogenesis and accumulation of lipid droplets (Schneider et al, 2016), so they would be expected to be upregulated at an early sebaceous cell stage. A 2015 study by Dahlhoff et al analyzed the lipid droplet protein profile of SZ95 to see which proteins are expressed on sebaceous lipid droplets in high abundance (defined by a spectral count of at least 10 in mass spectrometry quantitation [see Zhou et al, 2012 for the explanation of mass spectrometry spectral counts]). The study found that the only perilipins that are expressed in high abundance in SZ95 are PLIN2 and PLIN3. However, immortalized cells, like the SZ95, are probably more likely than normal sebaceous cells to have an “agenda” favoring excess lipid production. In any case, sebaceous lipid droplets in humans, hamsters, and probably all mammals, express perilipin A, which means that sebaceous lipid droplets are supposed to be broken down by perilipin A, and therefore that magnesium is required for the smooth flow of sebum from dermis through epidermis to skin surface.)

Furthermore, the transition of sebum from a stream of large lipid droplets in the dermis to a stream of lipid constituents approaching the skin surface can be viewed as a 2-stage lipolysis cascade—the first stage being the above-described breakdown of lipid droplets to micro-lipid droplets, and the second stage being the breakdown of the lipids in the droplets to useful lipid constituents, such as triacylglycerides to free fatty acids. Both lipolysis stages are tied to PKA phosphorylation of perilipin A (A. Marcinkiewicz et al, 2006; Wang et al, 2009). Lipolysis requires magnesium-activated protein kinase phosphorylation of the relevant lipases as well. For example, in mouse adipocytes, PKA phosphorylation of perilipin A results in the recruitment, phosphorylation, and activation of adipose triglyceride lipase (Sahu-Osen et al, 2015). And in mouse adipocytes and Chinese hamster ovary cells, PKA phosphorylation of perilipin A is essential for the translocation of hormone-sensitive lipase (HSL) to the lipid droplet surfaces (Sztalryd et al, 2003). Additional lipolysis examples are discussed in Bickel et al (2009). Sebaceous cell lipid droplets with activated perilipin A would be expected similarly to recruit and activate lipases for the full lipolytic sequence. In normal human skin, the sebaceous glands and external root sheaths of the hair follicles have been shown to express lipase (Jimenez-Acosta et al, 1990).

Returning to the issue of exactly where along the sebum path—from the sebaceous gland, through the sebaceous duct, through the follicular canal—the numerous sebaceous lipid droplets are supposed to break down to micro-lipid droplets, and the micro-lipid droplets to usable lipids: it turns out that if sufficient magnesium is available, the entire cascade of breakdown events should be able to occur either intracellularly, within sebaceous cells before holocrine burst, or extracellularly, while in transit to or within the sebaceous ducts or hair follicles. Even if the sebaceous system is designed to trigger the cascade of breakdown events intracellularly, the system seems to allow for the backup strategy of extracellular breakdown in the case of missed timing or temporary magnesium insufficiency. This backup option would prevent or dissolve clogs.

The evidence for this option is that extracellular protein kinase phosphorylation, such as in bloodstream or secretions, has been discovered in recent years to be physiologically important and not uncommon in mammals (Yalak and Vogel, 2012; Klement and Medzihradzky, 2017). And the types of proteins that have been found to be modifiable by extracellular phosphorylation include proteins involved in lipid transport and homeostasis (Klement and Medzihradzky, 2017). Furthermore, PKA is one of the protein kinases that has been shown to phosphorylate extracellularly a number of target proteins (Cabrera-Pastor et al, 2016). And ATP, which is a necessary component of PKA phosphorylation, can also be synthesized extracellularly or released for activity into extracellular spaces (Valak and Vogel, 2012). Physiological events that lead to an increase in extracellular ATP include cellular damage (Yalak and Olsen, 2015), and holocrine burst of the sebaceous cell would seem to be a case of cellular damage.

This information indicates that magnesium could probably successfully trigger the breakdown of large lipid droplets that have already left the sebaceous cell and that are clogging the sebaceous duct. If ample magnesium is administered, the necessary components for dissolving the clogs are present.

In Addition, Magnesium-Triggered Protein Kinase Phosphorylation Inactivates the Proteins that Most Directly Induce Lipogenesis in the Sebaceous Glands

Protein kinases are reversible molecular switches: they are enzymes that use metal catalysts—almost always magnesium—to phosphorylate proteins, transferring a phosphate from ATP to a target protein; then enzymes known as phosphatases later remove the phosphate from the phosphorylated protein. There are about 500 different kinds of protein kinases in the body, almost all of which rely on magnesium. About one-third of the proteins in the body routinely undergo phosphorylation/dephosphorylation by one or more protein kinases. Protein kinase phosphorylation activates some of these proteins, whereas it inactivates others, and then phosphatases do the reverse. Key lipogenic proteins in the sebaceous glands that are inactivated by magnesium-catalyzed phosphorylation are the following:

LXR-alpha: In the case of some nuclear receptors, protein kinase phosphorylation inactivates them, terminating the signaling response that the receptors would otherwise have to their ligands by inducing conformational changes that result in DNA dissociation or decreased ligand affinity (Rochette-Egly, 2003). The nuclear receptor LXR-alpha, the major inducer of sebaceous lipogenesis discussed above, is a protein that undergoes magnesium-catalyzed PKA phosphorylation (Chen et al, 2006) in such a way that lipogenesis is inhibited: PKA phosphorylation of LXR-alpha inhibits LXR-alpha-induced SREBP-1c expression, as shown in rat liver (Yamamoto et al, 2007).

SREBPs: The SREBP pathways drive fatty acid/triacylglycerol synthesis and squalene/cholesterol synthesis in the sebaceous glands. There are 3 SREBP isoforms. SREBP-1a and SREBP-1c initiate the series of biochemical reactions that lead to the production of fatty acids/triacylglycerols. SREBP-2 and SREBP-1a initiate the series of biochemical reactions that lead to the production of squalene/cholesterol. Each SREBP-driven biochemical pathway of lipid synthesis has a rate-limiting step, defined as the slowest step in the pathway and the one that determines the overall rate of the other reactions in the pathway. For the SREBP-1c and SREBP-1a pathways of fatty acid/triacylglycerol synthesis, the rate-limiting step is the enzyme ACC (acetyl coA carboxylase), and for the SREBP-2 and SREBP-1a pathways of squalene/cholesterol synthesis the rate-limiting step is the enzyme HMG-coA-reductase. The 3 SREBPs and the 2 rate-limiting enzymes represent key therapeutic blocking points for inhibiting sebaceous lipogenesis. Magnesium helps suppress activity of all 5 of these proteins.

SREBP-1a and SREBP-1c undergo magnesium-catalyzed PKA phosphorylation in a way that inactivates them, as shown in liver (HepG2) cells (Lu and Shyy, 2006). Dong et al (2014) confirmed that PKA phosphorylation of SREBP-1a and SREBP-1c inhibits transcriptional activity of nuclear SREBP-1a and SREBP-1c. SREBP-1c, additionally, and SREBP-2 undergo phosphorylation by another protein kinase, AMPK (adenosine monophosphate-activated kinase), in a way that inactivates them (Li et al, 2011). Magnesium catalyzes AMPK (Littler et al, 2010).

ACC: Magnesium-catalyzed AMPK phosphorylation of ACC inhibits it (Hardie and Pan, 2002), inhibiting the production of triacylglycerols. AMPK and ACC are detected in sebaceous glands (Smythe et al, 1998).

HMG-coA-reductase: Magnesium-catalyzed AMPK phosphorylation of HMG-coA-reductase inhibits it (Friesen and Rodwell, 2004; Rosanoff and Seelig, 2004), inhibiting the production of squalene. HMG-coA-reductase is detected in sebaceous glands (Smythe et al, 1998).

PLIN2: Magnesium can suppress activity of the apparently lipogenesis-promoting lipid droplet protein PLIN2: magnesium-dependent AMPK phosphorylation of PLIN2 triggers its degradation (Kaushik and Cuervo, 2016).

Magnesium Seems to Have a Balanced Role in the Less Direct Influences on Lipid Biosynthesis

The LXR-alpha/SREBP system of biochemical pathways directing lipid synthesis in the sebaceous glands presents a fairly clean semi-linear picture. But the total picture of all the biochemical pathways in the body that can indirectly affect lipid synthesis in the sebaceous glands looks more convoluted and is less precisely understood.

Magnesium, in addition to having the above-mentioned direct influences on key proteins of the SREBP system, has less direct routes of influence on the SREBP system. A number of other proteins whose activation or inactivation is dependent upon magnesium lie along biochemical pathways linked eventually via a series of steps to the SREBPs. However, the more remote the magnesium-dependent biochemical actions are from the SREBPs, the less consistent or assessable is the net effect of magnesium from these actions on the SREBPs. This is because simultaneous conflicting magnesium-dependent signals can be generated within a complex system of pathways that has many inputs and feedback loops involving magnesium components. Many of the proteins that influence lipid production in sebaceous or other cells are associated with cellular growth and the cell cycle in general; and maintaining sebaceous lipid homeostasis is not the body's highest priority. So while overall magnesium appears to significantly lower lipogenesis in the sebaceous glands, this beneficial effect for acne sufferers likely occurs via the more direct magnesium-dependent biochemical inputs to the SREBP pathways rather than via the more indirect remote ones.

An example, relevant to recent research on acne, surrounds the mTOR protein, especially in relation to the FOXO1 protein. Activation of mTOR can lead to activation of SREBP and consequent lipogenesis, whereas activation of FOXO1 leads to inhibition of SREBP and decreased lipogenesis. Inhibition of FOXO1 in parallel with activation of mTOR Complex may be a factor in acne (Melnik and Zouboulis, 2013), and the inhibition of nuclear FOXO1 in skin is correlated with acne (Agamia et al, 2016). Magnesium, however, does not appear to directly activate either mTOR or FOXO1. In fact, mTOR is one of the rare protein kinases that is preferentially activated at its catalytic site by manganese rather than by magnesium (Michels et al, 2010; Sato et al, 2009). But both mTOR and FoxO1 can be activated and inactivated indirectly by pathways involving magnesium. Protein kinase B (PKB, also called Akt) is magnesium-catalyzed and, in the presence of insulin, can phosphorylate and activate mTOR activation as well as phosphorylate and inhibit FOXO1. However, magnesium appears to lower insulin levels (see Barbagallo et al, 2007; Hruby et al, 2013), which would seem to partially counter the effect of Akt/PKB on mTOR. Meanwhile, magnesium-catalyzed AMPK inhibits mTOR indirectly, by phosphorylating 2 of its regulatory proteins, raptor and TSC2, which then inhibit mTOR (Gwinn et al, 2008; Portsmann et al, 2008). But TSC2 can also be phosphorylated by a number of other different kinases, each with different consequences (Inoki et al, 2006). Furthermore, magnesium activates the PP2A-phosphatase-activator (PTPA) (Jordens et al, 2006), which activates the phosphatase PP2A to dephosphorylate many proteins, including Akt/PKB and FOXO1. The result is inhibition of Akt/PKB (Kuo et al, 2008), and activation of FOXO1 (Yan et al, 2008), which then inhibits the SREBPs and so helps suppress lipogenesis. But then magnesium-catalyzed-PTPA-activated PP2A also activates ACC and HMG-coA-reductase, which are steps in lipid synthesis. These details show only a partial scenario of the very complex system of indirect pathways potentially affecting lipid synthesis in the sebaceous glands.

There are many additional “miscellaneous” proteins that, as components of various biochemical pathways, can be directly or indirectly activated or inactivated by magnesium and affect signals reaching the SREBPs. But the entangled relationships between all these different proteins and pathways have not been fully elucidated yet by researchers.

In sum, in the pilosebaceous units, LXR-alpha seems to be a master regulator of sebaceous lipogenesis, turning on or off the SREBP pathways of lipid synthesis. Although magnesium’s remote influences on this system may balance out to low or even zero, magnesium’s most direct influences on this system seem clearly anti-lipogenic.

Studies on Magnesium Deficiency Indicate that Magnesium Lowers Lipid Synthesis

In liver cell culture studies on the role of magnesium in lipid regulation, magnesium deficiency leads to an increase in lipogenesis-promoting SREBP-2 and a decrease in

lipogenesis-inhibiting Insig-2, in alignment with the medical literature showing a 2-fold increase in liver triglyceride content with magnesium-deficient diets (Etwebi, 2011). Magnesium deficiency, common in modern societies, appears to be a risk factor for increased lipogenesis, indicating that sufficient magnesium may lower lipogenesis.

In Summary, Taurine and Magnesium Decrease Sebaceous Lipogenesis

TABLE 1: Effects of Taurine and Magnesium on the Activity Levels of Proteins Most Directly Controlling Lipid Production and Lipid Flow in the Sebaceous Glands

<u>Proteins</u>	<u>Ideal Situation*</u>	<u>Real Situation</u>	
		<u>Tau</u>	<u>Mag</u>
LXR-alpha	down	down	down
Insig1	up	(no info)	
Insig2	up	up	
SREBP-1a	down		down
SREBP-1c	down	down	down
SREBP-2	down	down(?)	down
ACC	down		down
HMG-coA-reductase	down		down
PLIN1a	up		up
PLIN2(?)	down		down
PLIN3(?)	down	(no info)	

[*Ideal Situation refers to what would seem to be ideal for an acne patient undergoing treatment. A question mark indicates some uncertainty in the data.]

DIAGRAM 1a: Biochemical Pathways of Sebaceous Lipid Synthesis

LXR-alpha linked — [directs SREBP-1c path, influences SREBP-2 path]

Squalene/Cholesterol Synthesis Pathway [abbreviated] —

Activated via SREBP-2 or SREBP-1a

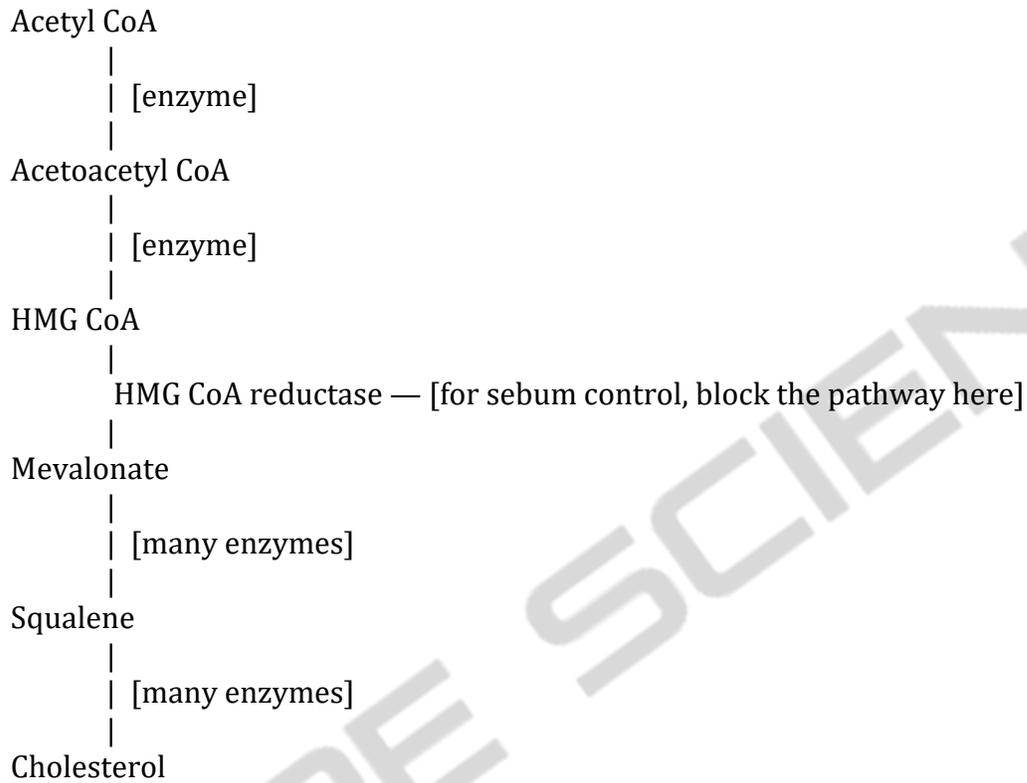
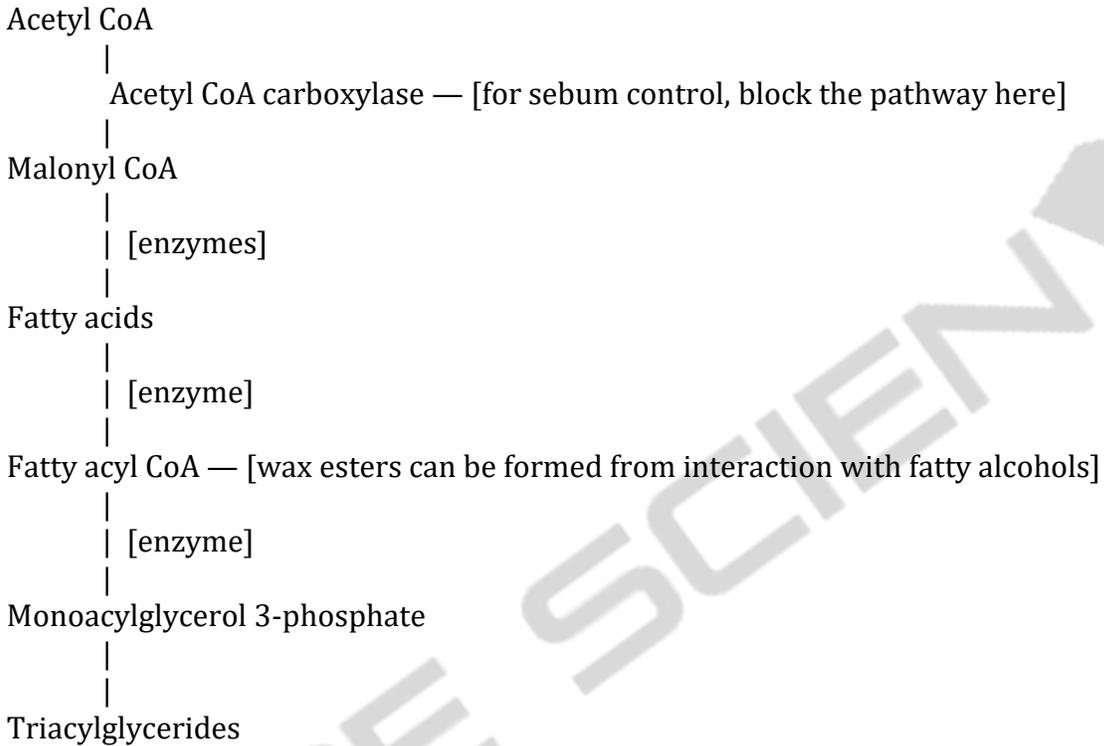


DIAGRAM 1b: Biochemical Pathways of Sebaceous Lipid Synthesis

LXR-alpha linked — [directs SREBP-1c path, influences SREBP-2 path]

Fatty Acid/Triacylglyceride Synthesis Pathway [abbreviated] —

Activated via SREBP-1c or SREBP-1a



Reference Note: These pathway Diagrams 1a and 1b were constructed using some of the many pathway diagrams and pathway bits of information widely available online. Some parts of the resultant diagrams are abbreviated for clarity.

Taurine and Magnesium May Have Additional Benefits for Treating Acne

Taurine and Magnesium Might Possibly Reduce the Viscosity of Sebum, Helping to Prevent Clogging

Taurine and magnesium in the pilosebaceous units might play a role in reducing the viscosity of sebum, if these micronutrients come into contact with sebum—a speculative suggestion that could be investigated. Lowered viscosity might reduce the risk of clogging.

Viscosity-lowering studies on taurine include the following: Taurine, compared to other dipolar ions tested in a study by Tsangaris and Martin (1965), has very low viscosity in aqueous solution. Taurine significantly reduced the levels of whole blood viscosity in a study on rats and type-2 diabetes (Zhang et al, 2010, abstract). Taurine levels increase dramatically in hibernating vertebrates under conditions of increased blood viscosity caused by lower core body temperature, helping to prevent hyper-coagulative states (Miglis et al, 2002).

Viscosity-lowering studies on magnesium include the following: Magnesium has been shown to help lower blood viscosity (Dou et al, 2009). There does not appear to be information yet on whether the pilosebaceous units accumulate large amounts of magnesium when it is abundant in the body.

Taurine Might Help Heal Acne Wounds

Taurine might also help with wound healing, clearing up the lesions of acne at a faster pace than otherwise. Degim et al (2002) and Dincer et al (1996) found that locally administered taurine in mice significantly increased wound tensile strength, which suggested that taurine might be effective in wound healing. The proposed mechanism of both studies was taurine's suppressive effect on lipid peroxidation. The taurine of the Degim et al study was in an experimental topical gel formulation. Potential development of a topical taurine-magnesium gel for acne treatment in humans is discussed in Part VI.

Taurine Might Help Mitigate the Depression and Anxiety Caused by Acne

Taurine has been shown in rats subjected to chronic unpredictable mild stress to have significant anti-depressant and anti-anxiety effects (Wu et al, 2017). If taurine also has this effect in humans, then possibly it could help halt the “vicious-cycle” component of acne, in which acne patients with social avoidance brought on by the anxiety and depression of having to face the world with acne stay home a lot, where they often develop compulsive picking of lesions, worsening the lesions and subsequently becoming even more depressed and anxious.

Taurine with Might Mitigate Scarring

The significant reduction in severe acne scarring experienced by one volunteer on taurine-magnesium supplementation is probably related to the important function of taurine as an osmolyte, helping to regulate and replenish water in cells, and to the role of magnesium ions as electrolytes, helping to hydrate cells.

Taurine and Magnesium are in Some Ways Synergistic

The relationship between taurine and magnesium in the human body is not fully known yet. Taurine is an important osmolyte in cells (Huxtable, 1992), and magnesium is also referred to in at least one study as an osmolyte (Roche et al, 2006). Whether these two micronutrients work together in an osmolyte capacity could be investigated. Taurine is believed by some researchers to help regulate magnesium homeostasis (Durlach and Durlach, 1984, abstract). As mentioned in the Introduction, taurine facilitates the transport of magnesium ions across cell membranes (Human Metabolome Database). It is possible that there are additional synergistic relationships between taurine and magnesium that affect acne.

PART IV: HOW SUBOPTIMAL TAURINE INTAKE COULD LEAD TO SERIOUS TAURINE DEFICIENCY IN THE PILOSEBACEOUS UNITS

The Thrifty Phenotype Hypothesis and the Triage Theory Are Applicable to Taurine

According to the “thrifty phenotype hypothesis” (Hales and Barker, 1992; Barker, 1997; Hales and Barker, 2013; Hoet et al, 2000), poor fetal nutrition and poor early post-natal nutrition lead to survival-ensuring strategies by the body, in which the nutrients in short supply are diverted to critical organs at the expense of peripheral tissues. According to the “triage theory” (Ames, 2006), even modest micronutrient deficiency initiates the body’s triage (emergency) strategy of diverting micronutrients from tissues of secondary importance to those of primary importance. The thrifty phenotype hypothesis and triage theory imply that a lengthy deficiency of taurine would lead to dietary taurine being conserved mainly for the more critical tissues, such as the heart, eyes, brain, liver, and pancreas.

In humans, the pilosebaceous units appear to be tissues of secondary importance, so during times of dietary taurine deficiency, much of the body’s taurine that would normally go to the pilosebaceous units instead likely gets diverted to more critical tissues. Taurine can be interchanged between organs (Huxtable and Lippincott, 1983), so during times of taurine deficiency, some of the taurine already present in the pilosebaceous units might even be transferred out to the more critical tissues, further depleting the pilosebaceous units.

In cases of chronic taurine insufficiency beginning early in life and lasting throughout childhood, the sebaceous glands might consequently be predisposed to

producing excess lipids. Then when the onset of puberty spurs a significant increase in androgen production, the sebaceous glands would likely respond by producing an acne-causing quantity of lipids, marring the teenage skin.

The Distribution of Taurine During Deficiency May Be Modulated by Taurine Transporters

Taurine transporters on cell membranes transport taurine from the bloodstream into the cells, but not evenly among all tissues. Taurine content is not the same from tissue to tissue (Huxtable, 1992; Shimada et al, 1984), and varying dietary taurine intake can affect taurine content of different tissues differently (Satsu et al, 2002). If the density of taurine transporters is low in a particular tissue, a large amount of taurine is unlikely to accumulate in its cells.

The body's basic pattern of distribution of taurine among different tissues might be formed early in life by the expression of taurine transporters at different levels in different tissues. Shortages of taurine might lead to the selective up-regulation or down-regulation of taurine transporters in different tissues in order to redistribute the body's taurine supply such that the most critical tissues obtain taurine at the expense of less critical tissues.

Taurine Has at Least One Major and One Minor Transporter

The major known transporter protein for taurine is TauT (gene name SLC6A6 in the solute carrier family). This transporter has high affinity for taurine, although it is not completely exclusive to taurine, because it also binds the [3H]GABA neurotransmitter, but with low affinity (Tomi et al, 2008; Zhou et al, 2012). Taurine can also be transported, at least in hepatocytes, by the GABA transporter GAT2 (SLC6A13) (Zhou et al, 2012). Taurine has another transporter protein, the PAT1 protein (gene SLC36A1), which is at high levels in intestine and brain and is known to transport taurine across the intestinal brush-border membrane for absorption into the bloodstream (Anderson et al, 2008). PAT1 is not highly specific for taurine, as is TauT, because it also transports GABA, glycine, and various other chemicals (Metzner et al, 2005). (Note: The acronym PAT1 is used in the biological literature for different unrelated biological entities. The taurine transporter PAT1 is distinct from a protein with that same acronym that is associated with the perilipin gene family. The perilipin-related "PAT1" is not referred to by that acronym in the present paper even in the discussions about perilipin.)

There May Be a Dearth of Taurine Transporters in the Pilosebaceous Units of Many Modern-Day Humans

Taurine transporters in the pilosebaceous units per se do not appear to have been studied yet. One study (Janeke et al, 2003) that analyzed human skin for the presence of TauT protein did not find any TauT in the dermis (which would include most of the pilosebaceous unit), only the epidermis. The skin that was analyzed,

however, was not from face or any other of the acne-prone areas, and it included, for example, fetal palm, which lacks sebaceous glands. Another study (Collin et al, 2006) did detect TauT in dermal tissue of human scalp. And a study by Warskulat et al (2008) found that human dermal fibroblasts express TauT mRNA. Since taurine can be taken up quickly and at high levels by cells in the pilosebaceous units (as shown in animals), it is obviously efficiently transported across pilosebaceous cell membranes some way, either by TauT or a combination of transporter types and/or unknown mechanisms. It is possible, for example, that the PAT1 transporter also transports taurine across membranes in the pilosebaceous units; PAT1 transporter has been detected in rat skin (Sundberg et al, 2008).

There may be a dearth of TauT or other taurine transporters in the pilosebaceous units of most modern-day humans who chronically receive suboptimal amounts of taurine, compared to the pilosebaceous units of humans who have had ample taurine throughout life.

Taurine Transporter Level Fluctuates

It is unclear how quickly a down-regulation of taurine transporters in skin could be reversed. Tissue expression of taurine transporters seems very flexible. Short-term fluctuations can occur rapidly because taurine is an osmolyte, and so taurine transporters are acutely up-regulated or down-regulated in response to tonicity of cellular environment (Ito et al, 2004), forcing rapid change in taurine concentrations to preserve cellular water volume while regulating ion flux. Short-term fluctuations of taurine transporters in tissues probably also occur to solve short-term needs for taurine for tissue-specific functions, such as the need by the liver to form taurine-conjugated bile salts when excess fat is consumed. Longer-term patterns of fluctuations in taurine transporters in different tissues have apparently not been measured. They may occur as a method by which the body prioritizes the allocation of taurine among the different tissues in response to taurine availability.

A Goal With Acne Treatment Could Be To Stimulate the Up-Regulation of Taurine Transporters in the Pilosebaceous Units and the Uptake of Taurine by the Transporters

A dearth of taurine transporters in the pilosebaceous units caused by chronic taurine insufficiency is likely to be reversible to some extent by providing a surplus of taurine to the body to stimulate the up-regulation of taurine transporters even in tissues of secondary importance. Indeed, acne cleared dramatically in volunteers when a surplus of taurine was provided with magnesium.

Magnesium likely stimulates uptake of taurine by TauT. TauT is a gated transporter, and taurine flows both in and out of the cell via TauT. Protein kinase phosphorylation of TauT influences both taurine uptake and efflux. The TauT protein has a series of phosphorylation sites for different protein kinases, particularly PKA, PKC, and possibly CK2 (Lambert and Hansen, 2011). PKA, which is

activated by magnesium, leads to increase uptake of taurine by TauT (Lambert and Hansen, 2011). PKC, however, which appears to be strongly preferentially activated by manganese rather than magnesium, leads to decreased uptake of TauT (see Yahuaca et al, 2000; Sidoryk-Wegrzynowicz et al, 2011). (CK2, generally catalyzed by magnesium, regulates various aspects of taurine homeostasis; but whether CK2 directly phosphorylates TauT, and if so whether such phosphorylation activates or inactivates TauT, is not clearly known yet.) Someone prone to acne should probably not take a higher dose of manganese than is essential. Magnesium is the synergistic mineral metal for taurine for acne.

A Consequence of Serious Taurine Deficiency in the Pilosebaceous Units May Be Uneven Distribution of Taurine Among Units, Leading to Variableness of Acne

Acne is not only variable among individuals but also within a given individual: acne is uneven; the individual with acne never knows where on the skin the next breakout will occur. In the study by Lobo et al (2001), the density of taurine in sebocytes was very variable among the different sebocytes. This study was of dog and rat skin, and it was not clear whether the uneven density was due to taurine deficiency in these laboratory animals or to some other reason. But if humans experience the same unevenness of taurine content in sebocytes, due to taurine deficiency in the pilosebaceous units, it might explain why the clogging among pilosebaceous units is uneven.

PART V: EVIDENCE THAT TAURINE INTAKE IS OFTEN SUBOPTIMAL IN MODERN DIETS

This part of the paper looks at different lines of evidence to determine whether humans living in agricultural (i.e., non-natural) societies have suboptimal intake of taurine that could affect their risk for acne. A paragraph on magnesium intake is included at the end of this part.

Requirements for Taurine Intake for Maintaining Pilosebaceous Health May Have Increased with Modern Diets

In order to prevent or counteract acne, taurine may be needed even more by individuals with agricultural diets than hunter-gatherer diets, because agricultural diets appear to stimulate greater sebum production. There may be a causal link between agricultural diets and excess androgen production, leading to excess lipogenesis in the sebaceous glands and consequent acne (Cordain, 2005, 2006; Melnik et al, 2013). Major dietary culprits, according to Cordain (2005, 2006) and Melnik et al (2013), are non-human milk and high glycemic load. Cordain (2006) discusses how these dietary factors can influence the cascade of hormones that influence acne, pointing out, for example, that the high glycemic foods of Western diets are generally high insulinemic foods, and that insulin stimulates the synthesis

of androgens. Non-human milk can cause various problems related to human acne. Melnik (2012) emphasizes that milk is not a simple food, but rather an endocrine signalling system specific to its source species that in humans activates mTORC1 (mammalian target of rapamycin complex 1), which can activate increased sebaceous gland lipogenesis (Melnik and Zouboulis, 2013). In one study, patients who switched to a non-dairy, low-glycemic diet (i.e., more Paleolithic diet) had a significant reduction of acne (Kwon et al, 2012).

Agricultural diets probably increase the need for taurine in the pilosebaceous units to help halt the excess lipogenesis induced by these diets, but they provide significantly less taurine than did ancestral hunter-gatherer diets, as described in the following section.

Agricultural Diets on Average Have Lower Levels of Taurine

Natural Sources of Taurine in the Diet Come from Animals Not Plants

Dietary taurine for humans comes primarily from meat, fish, and the milk of humans and some domesticated mammals. Taurine is present at some level in all meat and seafood tested (Laidlaw et al, 1990; Spitze et al, 2003), but taurine levels can differ dramatically among different cuts of meat (Purchas et al, 2004). In poultry, for example, dark meat rather than light meat is by far the richer source of taurine (Laidlaw et al, 1990; Spitze et al, 2003). The production system of raising animals for food can affect taurine levels; in one study, pasture-fed stock were higher in taurine than feedlot-fed stock (which were primarily grain- and potato-fed) (Purchas and Busboom, 2005). The method of storage or cooking can also alter taurine levels; for example, boiling meat or icing fish muscle can significantly degrade taurine content (Rana and Sanders, 1986).

Examples of taurine levels of various meats/seafood consumed by humans and animals are as follows (in mg/100g edible portion; Laidlaw et al (1990)): chicken light meat, broiled 15 +-4; chicken dark meat, broiled 199 +-27; turkey light meat, roasted 11 +-1; turkey dark meat, roasted 299 +-52; beef, broiled 38 +-10; pork loin, roasted 57 +-12; picnic ham 50 +-6; salami 59 +-8; beef bologna 31 +-4; tuna canned chunk light 39 +-13; tuna albacore 42 +-13; whitefish cooked 172 +-54; shrimp cooked 11 +-1; shrimp raw 39 +-13; oyster raw 396 +-29; clam raw 520 +-97; mussel raw 655 +-72; scallop raw 827 +-15.

Egg whites appear to have almost no taurine, although egg yolks have a little (Spitze et al, 2003). Taurine content of milk depends on the source species, as discussed below in the subsection on milk for babies. Taurine contents of cheese, cottage cheese, and yogurt from cow's milk are typically very low (Spitze et al, 2003).

Numerous plant foods have been tested for the presence of taurine, including fruits, vegetables, nuts, cereals, legumes, and all results have turned up essentially negative (Laidlaw et al, 1990; Spitze et al, 2003), or sometimes a trace, with the

exception of goji berries (Xie and Zhang, 1997, abstract), and cactus pear fruits (detectable in some samples at levels greater than 11mg per 100g portion by Fernandez-Lopez et al (2010), but not detectable by Ali et al (2014)). It is extremely unusual for a plant to contain taurine.

Ancestral Hunter-Gatherer Diets Probably Provided Much More Taurine than Agricultural Diets

The amount of taurine obtained in natural ancestral hunter-gatherer human diets depended on the amount of meat/fish in the diet. And for infants and young children, the amount of taurine in diet depended as well on the amount in human breast milk, which depended partly on the amount of meat/fish eaten by the mother and partly on the amount synthesized internally by the mother, which depended partly on the amount of cysteine, and methionine, and vitamin B-6 in her diet.

Most of the information on natural hunter-gatherer diets that is referred to in this paper comes from the work of Eaton and Konner (1985; 2010), who analyzed anthropological data on Paleolithic and 20th-century hunter-gatherers. Ancestral hunter-gatherer diets were apparently much more meat-based than were diets after the switch to agriculture and animal husbandry: the amount of animal flesh in the ancestral hunter-gatherer diet, as a percentage of total food energy (calories), is estimated to have ranged from 35% to 65% (Eaton and Konner, 2010). The percentage of meat and fish in most agricultural diets has been much less, as explained by Eaton and Konner (1985): "Agriculture markedly altered human nutritional patterns: over the course of a few millennia the proportion of meat declined drastically while vegetable foods came to make up as much as 90 per cent of the diet. This shift had prominent morphologic consequences; early European Homo sapiens sapiens, who enjoyed an abundance of animal protein 30,000 years ago, were an average of six inches taller than their descendants who lived after the development of farming." The nutritional quality of meat from free-living animals, such as those caught by hunter-gatherers, may also have been much better, having more protein per unit weight and less fat (Eaton and Konner, 1985). Whether wild game is also higher in taurine does not appear to have been measured yet. In any case, since taurine comes from animal flesh, and not from plants, the average amount of taurine an individual consumed in an ancestral hunter-gatherer society, especially as a percentage of total energy intake, would have been much greater than in a post-hunter-gatherer society. (Note: Theories on ancestral hunter-gatherer diets are still debated; although the heavily meat-based theory presented by Eaton and Konner is not considered fact by everyone, it is one of the main theories on ancestral human diets and for decades has been the one that made excellent scientific sense to me.)

Estimates of Average Taurine Intakes in Modern Industrialized Societies are Variable but Low

Rana and Sanders (1986) estimate that, from dietary analysis of a group of humans in England, the average human omnivore in a modern industrialized society consumes about 58mg of taurine per day. The range in their analysis was wide: 9-372mg/day. The taurine intake by vegans of their study was 0 mg/day. Laidlaw et al (1990) estimates taurine intake from the typical diet of an American 70kg omnivore male to be 123mg or 178mg, depending on which of 2 traditional diet plans is used; the estimate for a lacto-ovovegetarian is 17; and for a vegan 0.

In seafood-eating areas of the world the average dietary intake of taurine can be considerably higher than 58 mg/day, because some seafood is exceptionally high in taurine. In Japan, for example, in the district of Hokuriku, where fish intake is third highest of 9 districts in Japan, a country with one of the largest per capita consumptions of seafood, the average taurine intakes were 225.5mg/day for males and 162.6mg/day for females, and the highest taurine intakes were more than 1000mg/day, partly due to oyster-eating (Kibayashi et al, 2000). (I could not find data on the prevalence of acne in these areas.) Living in coastal regions does not necessarily translate to high average taurine intake though, even when the aquatic foods accessible to the region have very high taurine levels, as in the study by Zhao et al (1998): in China, in 4 coastal areas spanning 12 provinces, taurine intake among men had values of just 33.5, 40.5, 57.4, and 79.7mg/day (Zhao et al, 1998).

According to Cornet and Bousset (1999), taurine has a nice flavor to humans. So flavor of taurine per se would not be a deterrent to consuming it in modern societies. Most modern-day humans simply select many other taste-fulfilling or less expensive foods over the taurine-rich meat cuts and seafood, or become vegetarians.

An Estimate of Average Ancestral Hunter-Gatherer Dietary Intake of Taurine is Much Higher

My following “ballpark” estimate for taurine intake of ancestral hunter-gatherers is based on 4 assumptions: (1) The caloric intake of the women, who would have been physically active, would probably have been roughly 2400 Calories/day (non-lactating women) or 2900 Calories/day (lactating women); the caloric intake of the men, who would have been physically active, would probably have been roughly 3200 Calories/day. (2) The caloric content of the lean wild meat/fish was probably on average about 150 Calories per 100-gram portion. (3) From taurine content data on meat and fish, an estimate of taurine amount in an average 100-gram portion of meat/fish would probably be around 50mg. (4) On average, for ancestral hunter-gatherers, 50% of the daily caloric intake would have come from meat/fish. With these assumptions for, one could estimate that non-lactating ancestral hunter-gatherer women consumed roughly 400mg taurine per day (1200 cal meat per day x 50mg taurine per 150mg cal meat = 400 mg taurine per day); lactating women 483mg/day; men 533mg/day. These estimates are roughly 3-9 times higher than the average estimated taurine intakes of modern westernized omnivorous peoples.

Most contemporary non-Westernized populations, such as the Ache and Kitavans studied by Cordain et al (2002), do not derive 50% of their calories from meat/fish, so do not obtain the high dietary taurine levels that ancestral hunter-gatherers probably did, yet they apparently escape the disease of acne. According to the Cordain et al study, the Ache obtain 20% of their calories from meat (17% of which is from wild game), and the Kitavans derive only 10% of their calories from protein (which probably means fish, a staple of their diet). Individuals of these populations probably synthesize a functional level of taurine from good dietary supplies of cysteine, methionine, and vitamin B-6, such that, given their very low glycemic load, they can avoid getting acne. Although their taurine stores may not be optimal, they are not really insufficient for the situation.

Agricultural Diets May Also Be Lower in Cysteine, Methionine, and Vitamin B-6, which the Body Needs for Synthesizing Taurine

It is unclear how much taurine is normally synthesized in humans internally from cysteine, methionine, and vitamin B6—dietary micronutrients that are in many meats as well as plant foods. But internal synthesis of taurine may be lower in modern agricultural humans, on average, than it was in ancestral hunter-gatherer humans. Since ancestral hunter-gatherers ate more meat, they obtained more meat-derived cysteine, methionine, and vitamin B-6. Also, ancestral hunter-gatherers most likely ate a wide variety of plant foods, as did the 20th century hunter-gatherers not living at the extreme northern latitudes (Eaton and Konner, 1985); and a diet with a large variety of plant foods would likely include sufficient cysteine, methionine, and vitamin B-6 to satisfy the requirement for normal internal synthesis of taurine. By contrast, many people in agricultural societies do not eat a wide variety of fruits and vegetables. Cysteine, for example, is present in an assortment of fruits and vegetables, but in different amounts, depending on the plant species, and it is not even detectable in some staple foods such as potatoes and bananas (Demirkol et al, 2004). A diet relying on only a few staples rather than a wide assortment might not include foods sufficiently high in this particular micronutrient. Furthermore, refined grains compared to non-refined grains tend to be much lower in vitamin B-6 (Enright and Slavin, 2010). Modest vitamin B-6 deficiency is not uncommon in the U.S. (Morris et al, 2008). Studies on rats have shown that activities of the taurine-synthesizing enzyme CSAD are extremely sensitive to vitamin B-6 deficiency, resulting in little production of taurine from cysteine or methionine under such conditions (Sturman, 1973). Thus, not only are modern diets generally lower in dietary taurine, but internal synthesis of taurine may be generally lower.

Switching to a Vegetarian Diet Might Lead to Greater Acne, Unless that Particular Vegetarian Diet Has Lower Glycemic Load

Biomedical data on acne and vegetarianism are very scant, and general claims on websites about vegetarianism leading to either better or worse skin are unreliable. However, of note is that many people supportive of vegetarianism have reported on

the web that when they switched to vegetarianism they suddenly surprisingly broke out with acne. The sudden lack of dietary taurine would be expected to put a person at higher risk for some detrimental physiological effects, such as acne.

People without dietary sources of taurine still synthesize some taurine internally. It is not known how much cysteine, methionine, and vitamin B-6 would need to be consumed in diet by vegetarians or vegans in order to synthesize adequate stores of taurine. Many vegans and other vegetarians eat a wide variety of fruits and vegetables, and so probably get enough cysteine, methionine, and vitamin B-6 to synthesize at least marginal, although not optimal, levels of taurine. Plasma levels of taurine are slightly to moderately lower in vegans than in omnivores (Rana and Sanders, 1986). Differences in tissue levels of taurine between vegans and omnivores are not known. Tissue content of taurine can decrease over time while plasma levels stay the same, as shown in pregnant rats (Akahori et al, 1986), but whether this phenomenon is common in non-pregnant animals is not known. So it is difficult to tell how taurine-deficient vegans really are, since their tissue taurine levels are not measured.

In a study by Waldmann et al (2007), vegans tended to eat lower glycemic index foods than omnivores and had, on average, only a low to moderate glycemic load. Vegans also refrain from dairy. Since high glycemic load and dairy can lead to acne, avoiding these dietary factors could give the vegan some advantage in acne prevention, somewhat offsetting their insufficiency of taurine.

Taurine Availability for the Pilosebaceous Units Might Be Lower When Diets Are High in Glucose, Fat, and Salt

There are striking differences between ancestral hunter-gatherer diets and modern agricultural diets that can affect whether taurine in the bloodstream is actually made available to tissues of secondary importance such as the pilosebaceous units: 1) the high glycemic load of agricultural diets; 2) the high fat load; 3) the high salt load.

High glycemic load may result in extra taurine being taken up by the pancreas for the regulation of insulin release, at the expense of lower availability of taurine to less critical tissues. There are studies showing that taurine is present at high levels in the pancreatic islet cells (Carneiro et al, 2009), and that the transport of taurine into pancreatic beta-cells is important for the release of insulin (L'Amoreaux et al, 2009).

The relationship between taurine and fat load is partly known, because one of the primary known functions of taurine is to emulsify dietary fats by conjugating to bile acids and forming bile salts (Huxtable, 1992). If a diet contains extra fat, extra taurine is probably needed to process that fat. If after a high-fat meal taurine preferentially goes to the enterohepatic system, less taurine is available for tissues of secondary importance such as the pilosebaceous units.

There also seems to be some relationship between salt load and taurine availability. In a study on rats, diets high in both salt and fat (although not just salt) led to significantly greater taurine excretion by the kidneys (Mozaffari et al, 2006), leaving less taurine available for other tissues.

Extra taurine in the form of oral supplements may be needed by humans with modern agricultural diets in order to compensate for these evolutionarily novel dietary factors. Even when modern agricultural humans increase their meat consumption, as often happens when poor societies become more prosperous, the increased meat consumption does not necessarily lead to an increase in taurine availability for the pilosebaceous units, because it does not necessarily represent an increase in meat as a percentage of total caloric intake. In modern times, increased portions of meat are generally accompanied by increased portions of additional foods high in fat, carbohydrates, and salt, such as sauces, buns, or other starches. Furthermore, such meat is usually not lean, as is wild game. So with increased modern-day meat consumption, the taurine pool available to the pilosebaceous units does not necessarily increase, because the amount of taurine needed by the high-priority organs that have to process the extra fat, sugar, and salt is increased.

Early-in-Life Taurine Intake May Be Lower in Agricultural Societies

Human Fetuses Are At Risk For Insufficient Taurine if the Mother's Taurine Level is Low

The fetus has extremely low ability to synthesize taurine, so it depends on the mother for its source of taurine. The tissue concentrations of taurine in human placenta are 100-200-fold higher than in maternal blood (Norberg et al, 1998). Taurine transporters are at high enough density in the placental syncytiotrophoblast to ensure that the fetus by 24 weeks has higher levels of taurine in the bloodstream than the mother. By 9 days after birth, fetus and mother have roughly the same levels of taurine (Moriyama et al, 1987).

There are various ways that a fetus can end up getting only suboptimal levels of taurine. For example, low taurine levels in the pregnant woman result in low taurine levels in the fetus (Aerts and Van Assche, 2002), and a woman who eats little meat/fish may have suboptimal taurine levels.

A pregnant woman's sugar intake could affect fetal taurine levels. In rats, taurine levels in amniotic fluid decrease with increases in maternal intake of glucose (Gurekian and Koski, 2005). If this study is applicable to humans too, then average taurine levels in fetal amniotic fluid probably have declined in modern agricultural societies, since sugar intake is so much higher than it was in ancestral hunter-gatherer societies.

Maternal obesity appears to be a risk factor for low taurine transport to the fetus, because there is a significant reduction of TauT taurine transporters in the placentas of women who are obese (Desforges et al, 2013). Ancestral hunter-gatherer women were extremely unlikely to have been obese.

Maternal diet might also affect fetal taurine levels in indirect ways, if maternal glycemic load, fat load, and salt load affect taurine availability to the placenta. High glycemic load, fat load, and salt load are common in modern agricultural diets, not hunter-gatherer diets.

In light of the above factors, fetuses of agricultural women are almost certainly more likely than fetuses of ancestral hunter-gatherer women to have suboptimal levels of taurine.

Infants Obtain Taurine from Breast Milk, but the Taurine Content of Breast Milk is Variable Among Women

The average taurine content of breast milk of ancestral hunter-gatherer women was probably higher than that of breast milk of agricultural women because breast milk taurine content appears to correlate with meat/fish intake. Human breast milk is a rich source of taurine for babies; its taurine content is much higher than in plasma. Taurine content of human breast milk is highest shortly after giving birth, decreasing somewhat over the next few months. It is variable among women, showing a wide range both within a given population and between different populations in the world. Since the taurine level in the breast milk of a woman does not appear to vary much throughout the day (Clark et al, 1987), the variation in taurine levels of breast milk measured among different women seems to reflect real differences in levels. There have been many studies of taurine in lactating women in different parts of the world (the different methods used to measure taurine content might account for some of the variation in results).

The variation in average breast milk taurine content within a given population is often thought by the authors of the studies to reflect meat/fish intake. A study in Great Britain looking at extremes (Rana and Sanders, 1986) measured taurine in the breast milk of omnivores vs. vegans 4-6 weeks postpartum, and found that the taurine content of omnivores was 427 +/- 37.8 micromoles/liter, with a range of 191-683, whereas of vegans it was 277 +/- 28.4 micromoles/liter, with a range of 122-529. A study in Korea (Kim et al, 1996) comparing taurine content of breast milk of omnivores and lacto-ovovegetarians a few months postpartum measured omnivore taurine content of 248-434 micromoles/liter, whereas lacto-ovovegetarian taurine content of 153-418 micromoles/liter. In a study of urban and rural Mexican women (Pasantes-Morales et al, 1995, abstract), the difference between the subpopulations was believed to be due to the restricted consumption of meat by the rural women; urban women showed a range of 332-357 micromoles/liter and rural women 237-259 micromoles/liter. In a study of rural Chinese (Lee-Kim et al, 1998), the low level of taurine content among women was thought to reflect lower intake of animal

products due to economic circumstances; the taurine content of women a few weeks postpartum was 186 +-48 micromoles/liter and of women a few months postpartum 158 +-65 micromoles/liter, values among the lowest of populations studied.

The highest breast milk taurine content measured in the available international studies was from Ethiopian women 2-5 months postpartum (Svanberg et al, 1977): 761 +- 143 micromoles/liter in women with normal-weight infants, and 535 +- 61.1 micromoles/liter in women with infants of lower weight. Most Ethiopian women in the year of the study, 1977, were very poor; it was not made clear whether the particular women from the special urban clinic of this study had higher than normal intake of meat, or substantial intake of goat milk, which can be very high in taurine, or whether the high taurine values were partly a reflection of the methods of measurement used. Examples of variation in taurine content of breast milk in other populations around the world include women from Sweden (667 +-70 micromoles/liter; also from the Svanberg et al study); Ecuador (357.2 micromoles/liter; Baldeon et al, 2014); the United States (337 +-28 micromoles/liter; Rassin et al, 1978); Italy (301.1micromoles/liter; Agostini et al, 2000); and Spain (228 +-59 micromoles/liter for infants of normal size; Pamblanco et al, 1989). In a systematic review of taurine content of breast milk from around the world (Zhang et al, 2013), women in Asia were found to have higher levels of taurine than European or North American women (roughly 370 compared to 310 micromoles/liter). All in all, these studies show that the variation among women in taurine content of breast milk can be several-fold. Different infants with different mothers take in different amounts of taurine from breast milk, and some take in amounts less optimal than others.

Breast-feeding can protect the baby from early taurine insufficiency by providing taurine-rich food. Hunter-gatherer women who were studied in the 20th century were found to breast-feed their babies for at least 2 years and for up to 4 years. In Cordain's 2002 study on the absence of acne among non-westernized peoples, the Ache and Kitavans were showcased; both the Ache (Konner, 2004) and the Kitavans (Guyenet) breastfeed their babies for about 2 years.

Taurine Content in Milk for Babies from Some of the Domesticated Dairy Animals Can be Very Low

With the domestication of animals, women could shorten the period of breastfeeding and substitute animal milk for their own breast milk. (Many women around the world still did breastfeed for a long time, but many others opted to stop early, and 2-year breast-feeding is rare in Westernized countries.) At least 5 species of animal have been domesticated since ancient times for milk: cow, goat, buffalo, sheep, and camel. Taurine content in cow's milk is very low, and this is the milk most commonly ingested by babies in modern developed countries. Rassin et al. (1978) measured taurine content in cow's milk (during the stage of lactation when the milk is collected for human consumption, which is after 7 days) and found it to

be only 10 micromoles/liter, a small fraction of the taurine content in human breast milk. Values of taurine content in cow's milk from other studies include a range from undetectable (Cataldi et al, 2004) to roughly 1/6 that of the average measurement for human milk (Erbersdobler et al, 1984). Goat milk, on the other hand, is rich in taurine, with levels surpassing that of human milk, 362 micromoles/liter compared to 335 micromoles/liter in humans (Mehaia and Al-Kanhal, 1992, abstract), with some goat species having levels significantly greater (Cataldi et al, 2004), up to 909 micromoles/liter (Tripaldi et al, 1998, abstract). Buffalo milk (Italian) has taurine levels roughly equal to that of goat milk (Manzi and Pizzoferrato, 2013). Sheep's milk (from the stage of lactation after 7 days) is significantly lower in taurine than is most human milk, at 141 micromoles/liter (Rassin et al, 1978). Camel's milk is very low in taurine, only 13 micromoles/liter (Mehaia and Al-Kanhal, 1992, abstract).

Whether children raised on goat's milk grow up to have less acne than children raised on cow's milk does not appear to have been measured.

Taurine Content in Infant Formula Can be Low

Infants who were fed formula instead of their mothers' breast milk may not have received adequate amounts of taurine, depending on the year and brand of their formula. Formula became widely available for infants and older babies as a substitute for human breast milk and animal milk in the 1900s. The early formulas contained no taurine or only a trace of it. Taurine was recognized during the 1970s as essential for development, based on results from taurine deprivation experiments on cats, a species that cannot internally synthesize adequate amounts of taurine and must rely on dietary sources (see Sturman et al, 1978). During the 1980s taurine was added to pre-term infant formulas in Europe and the U.S. because pre-term babies cannot synthesize adequate taurine. Many companies that produced commercial infant formula began adding small amounts of taurine to standard infant formulas, and then later added larger amounts. In the 1980s, in a study in Germany by Erbersdobler et al (1984), the 24 milk-based infant formulas analyzed contained much less taurine than cows' milk. And taurine in term formula from the early 1980s from a London study showed only a trace of taurine (Wharton et al, 2004). Laidlaw et al (1990) measured taurine content of infant formulas and found it to be higher in the formulas than in cow's milk, but nowhere near the taurine content of average human breast milk. However, in 2000, in a study of 11 starting infant formulas from Italy, France, Netherlands, and Switzerland (Agostoni et al, 2000), 10 formulas had higher taurine levels than the average level in breast milk. But 6 follow-up formulas (for older infants) from Europe that Ferreira (2003) analyzed had taurine levels significantly less than levels in human milk. Furthermore, the most recent analyses of micronutrients in human milk fortifiers and preterm infant formulas specifically for very low birth weight infants show that, contrary to recommendations by the American Academy of Pediatrics Committee of Nutrition, taurine is absent from all the standard brands, liquid or powder (Koo and Tice, 2017).

Different regions of the world have different regulations regarding the addition of taurine to infant formulas. In the U.S., the recommendation in 1998 from the Life Science Research Office of the American Society for Nutritional Sciences (Raiten et al., 1998) was for zero minimum taurine in infant formula, and a maximum of 12mg/100kcal, roughly the upper limit of measurements of human breast milk. According to Ferreira (2003), European regulations specify that when taurine is added to infant formula the amount must be equal to or greater than 42 micromoles/100kcal, which is within the normal range for human milk. But in 2005, a medical position paper was published by researchers from Germany, the U.S, Australia, Brazil, India, Sweden, Singapore, Thailand, Mexico, Canada, Israel, France, Japan, and China, for the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (Koletzko et al, 2005), recommending that the addition of taurine to infant formulas be optional, with an upper limit of 12mg/100kcal and zero minimum.

The different commercial standard and nonstandard (e.g., organic) infant formula companies around the world have changed their ingredients over the years, and will probably continue to change them according to new scientific data or consumer pressures. Knowing which formula a child was fed during which years and tracking down the taurine amounts from those years may be helpful in assessing whether that child as an infant had adequate amounts of taurine. This information might be helpful in determining later acne risk, as explained below.

Early-in-Life Taurine Insufficiency Might Predispose Humans to Later Acne

Part of the thrifty phenotype hypothesis is that fetal or perinatal undernutrition brings out intrinsic physiological strategies for coping with this undernutrition, and that these strategies involve the re-programming of some physiological systems in ways that eventually lead to adult disease (Barker, 1997; Hoet et al, 2000). The development of teen acne may be partly a result of such re-programming. In the case of early-in-life taurine deficiency that becomes chronic, the emergency pattern of taurine distribution in tissues could become more dominant than the normal pattern.

Perinatal Animal Studies Show that Early-in-Life Taurine Deprivation Can Lead to Adult Disease

There have been a number of perinatal taurine deficiency studies in rats and mice in which, although no gross defects result (unlike in the embryonic case), long-term mechanisms are affected that lead to adult diseases, including: arterial blood pressure changes (Roysommuti and Wyss, 2014); susceptibility to sugar-induced hypertension (Roysommuti et al, 2009)); renal function alterations (Roysommuti et al 2010); alterations in autonomic nervous system responses (Khimsuksri et al, 2013); increases in lifetime oxidative stress (Lerdweeraphon et al, 2013). According to Lerdweeraphon et al (2013): “early life taurine depletion leads to

perinatal epigenetic programming that impacts adult physiological function". A number of taurine deficiency studies (e.g., Park et al, 2014; Aerts and Van Assche, 2002) even note a trans-generational effect of taurine deficiency, in which the adult offspring of taurine-deficient mothers can transmit the effects to the next generation.

Acne too may turn out to be a disease that is partly influenced by early-in-life taurine insufficiency and the consequent redistribution of taurine that takes place in the body to cope with low taurine supply.

In Sum, Many People in Modern Societies From Young Age On Have Insufficient Taurine Intake

Ancestral hunter-gatherer children probably consumed on average significantly more taurine per day in their diets than most children of the agricultural societies since then have consumed per day. A reduction in early-in-life taurine availability is likely to influence taurine transporter distribution. Since the pilosebaceous units are of secondary importance in humans, almost all of the taurine synthesized internally or obtained from diet during periods of taurine insufficiency is allocated to tissues more critical than the pilosebaceous units. This means that when the androgens at puberty stimulate enhanced lipogenesis in sebocytes, there is not necessarily enough taurine in the pilosebaceous units to prevent acne. Overcompensating for early-in-life taurine deficiency by later supplementing with high doses of taurine may be therapeutic.

Magnesium Intake Also May Be Much Lower On Average in Modern Agricultural Diets than in Ancestral Hunter-Gatherer Diets

Magnesium insufficiency is common in modern societies, even in the U.S. (Ford and Mokdad, 2003). Estimates cited in Rosanoff et al (2016) are that 50% of the US population has inadequate dietary intake of magnesium, including 89% of teenaged girls. There are many reasons why agricultural diets often lead to magnesium insufficiency. For example, magnesium is much lower in refined grains typical of Westernized diets than in natural grains (Enright and Slavin, 2010). Western diets are high insulinemic diets, and insulin has been shown to increase renal magnesium excretion, possibly causing magnesium depletion (Djurhuus et al, 1995). The variety of plant-derived foods in an individual's diet in most agricultural societies is less than the variety that has been measured in diets of hunter-gatherer societies, and the plant foods that are highest in magnesium might be overlooked in the selection of a relatively small assortment of foods. It would not be uncommon in modern societies, then, for pilosebaceous units to have insufficient magnesium.

PART VI: SUGGESTED DOSES OF TAURINE-MAGNESIUM FOR THE TREATMENT OF ACNE, PLUS OTHER THERAPEUTIC ISSUES

This part of the paper discusses the practical application of the above information on taurine-magnesium. Its main purpose is to recommend to a person with acne or to a dermatologist how oral taurine-magnesium might best be used to treat acne. Potential topical taurine-magnesium treatment is also discussed. Oral dose recommendations were determined from results of volunteers with acne. Homing in on therapeutic dose, up to a dose of 3g taurine with 300mg magnesium per day for mild to moderate acne, was relatively easy, because increasing the taurine dose by 1g from a base level usually made a marked therapeutic difference fast.

It is important to emphasize that for taurine-magnesium treatment of acne the taurine component is therapeutic at high doses, not low doses, whereas the magnesium component appears to be therapeutic even at relatively low doses (slightly below the RDA). The estimate for the best dose of taurine-magnesium for a given individual with acne should depend upon the individual's age, weight, maybe gender (men have thicker skin than women), and severity of acne. General recommendations are suggested following discussions on safety and pharmacokinetics of taurine.

Taurine Has a Good Safety Record at Therapeutic Doses

Taurine is considered by the Council for Responsible Nutrition (a Washington DC-based trade association for the dietary supplement industry) to be generally safe in amounts of 3 grams/day (for a 70-kg person) (Shao and Hathcock, 2008): "The OSL[Observed Safe Level] risk assessments indicate that based on the available published human clinical trial data, the evidence for the absence of adverse effects is strong for Tau at supplemental intakes up to 3 g/day. . . Although much higher levels of each of these amino acids have been tested without adverse effects and may be safe, the data for intakes above these levels are not sufficient for a confident conclusion of long-term safety, and therefore these values are not selected as the OSLs." Therapeutic taurine doses for various serious disorders, such as heart failure, hypertension, and diabetes, are up to 7 or more grams per day, for weeks or months (many of the clinical trials are summarized in Shao and Hathcock, 2008).

Pharmacokinetics Show that Oral Taurine is Rapidly Absorbed

In a pharmacokinetic study of taurine (Ghandforoush-Sattari et al, 2010), after a therapeutic dose of taurine (4g) was given to healthy volunteers in the fasting morning state, the plasma taurine concentration was measured as maximum at 1.5 (+ - 0.6) hr after administration. This result shows that taurine is absorbed and circulated in the bloodstream fairly rapidly, when it is swallowed on an empty stomach. Therefore, taurine might begin to be therapeutic within hours, if it is actually taken up by the relevant tissues.

Recommendations for Persons with Acne Are for High-Dose Supplemental Taurine with Low-Dose Supplemental Magnesium

Suggested Dosages of Taurine with Magnesium Are As Follows

Therapeutic Dose for Teens and Adults:

For small teen or small adult females (under 110 lbs) with mild to moderate acne, a good starting dose is probably taurine 2g/day with magnesium citrate 200mg/day, in divided doses: 1g taurine with 100mg magnesium citrate, twice per day. If after 2 weeks the acne is not visibly clearing, the taurine dose should be stepped up to 3g/day and the magnesium to 300mg/day. Medium to large females should probably start with taurine 3g/day with magnesium citrate 300mg/day, in divided doses. Total treatment time at these full doses should probably be at least 8 weeks, more likely 14 weeks, or until the skin is clear or near-clear for a few weeks. If the combination is effective against the acne, then a prophylactic maintenance dose of taurine 1-2g/day with magnesium 200mg/day could be taken for some period of time afterward. At the start of any acne breakouts thereafter, the higher dose of taurine-magnesium could be resumed until the acne resolves.

For teen or adult males with mild to moderate acne, a good starting dose is probably taurine 3g/day with magnesium citrate 300mg/day, in divided doses, for at least 8 weeks, more likely 14 weeks, or until the skin is clear or near-clear for a few weeks. If this combination is effective against acne, a prophylactic dose of taurine of 1-2g/day with 200mg magnesium could be taken for some period of time afterwards, and the higher dose resumed if there are future breakouts.

For severe acne in females or males, a good starting dose to help reverse the course of acne is probably taurine 3g/day with magnesium citrate 300mg/day, for at least 4 months and maybe for many more months. If this dose is effective, it could be followed by prophylactic doses of taurine of 2g/day with 200mg magnesium. Higher therapeutic doses of taurine, greater than 3g/day, and of magnesium, up to 400mg per day, might be considered for some patients with severe acne who have consulted with their physician regarding the higher dose. Treatment with a taurine-magnesium topical gel (yet to be developed, discussed below) along with the oral supplements might greatly enhance clearing in difficult cases.

If acne clears in a patient who is on a full dose of taurine-magnesium but then returns while the patient is on a lower prophylactic dose, the patient may need to resume taking a full dose for an indefinite period of time.

The taurine-magnesium supplements should probably be taken together on an empty stomach with water (at least half a glass). Taurine is water-soluble. And magnesium absorption may correlate with water absorption (Behar, 1974). Magnesium citrate is significantly more soluble and bioavailable than is magnesium oxide (Lindberg et al, 1990; Walker et al, 2003), and so may be the magnesium of

choice in the treatment. The empty stomach suggestion is to help ensure that the taurine is taken without high sugar/carbohydrate load, fat load, or salt load—which might otherwise cause some of the extra taurine to be sent to the pancreas, liver, or kidneys instead of being available to be distributed adequately to the pilosebaceous units.

Therapeutic Dose for Pre-Teens and Younger Children:

Most preteens experiencing their first onset of acne would probably need at least 1.5g/day taurine with 200mg/day magnesium, in divided doses. For greater effectiveness, doses could be raised incrementally as needed.

For young children, a pediatrician would need to be involved in determining safe doses per age, weight, and height of child. A child's dose of taurine for various medical disorders has been listed previously on some websites as 30mg/kg body weight/day, in divided doses.

Infants with acne may benefit from a special infant formula that has a relatively high level of taurine with adequate magnesium or from topical taurine-magnesium treatment.

Length of Time to See a Beneficial Effect

When taurine-magnesium treatment for a case of acne is begun, it might not necessarily appear to work immediately, as in the first few days. One reason is that the pilosebaceous units may not have sufficient up-regulation of taurine transporters to accumulate much taurine until they have detected a surplus of taurine for a more extended period of time. Also, the transit time for sebum should be taken into consideration when estimating the amount of time it should take to see a beneficial effect. The estimate for average sebaceous cell transition time by Downing and Strauss (1982) is 14 days, and the transit time of sebum in the follicular canals is 14 hours. Therefore, it can take a couple of weeks for a beneficial effect of taurine in the pilosebaceous units to be seen. Also, taurine-magnesium for acne works at a deep level, in the sebaceous glands and ducts, suppressing some lipogenesis and dissolving deep clogs. The anti-action there should lead to visible clearing. There's a lag time. The acne patients should initially give the taurine-magnesium treatment a try for 2 weeks before expecting to notice a definite benefit. Also, there may be a threshold effect, in that below a certain dose no visible effect is seen, so it is very important that acne patients on taurine-magnesium treatment remember to take all their doses. Once the pilosebaceous units are "trained" to accumulate taurine from the surplus in the bloodstream, there may be a dramatic clearing of acne. This "training" may be easiest to achieve in individuals who are young.

If after 2 weeks of taurine-magnesium treatment a benefit is not noticeable, the acne patient may need to increase the dose of taurine. The effect of increasing the taurine

dose by 1g/day can be dramatic (based on the experiences of some of the volunteers).

Side Effects

There appear to be no negative side effects from taurine supplements at doses up to 3g/day that are mentioned in the medical literature for treatment of various diseases and conditions, except in kidney patients, who may experience dizziness. Negative side effects of magnesium supplements at or slightly below the RDA can include laxative effects. The volunteers on taurine-magnesium supplementation were virtually free of side effects.

An Additional Multivitamin/Mineral Supplement Subset Might Be Helpful for Many Individuals with Acne on Taurine-Magnesium Treatment

While taurine and magnesium appear to be the key essential micronutrient components of the two main anti-acne mechanisms of action, other micronutrients that indirectly help support these two anti-acne mechanisms or that support the functioning of taurine and magnesium in the pilosebaceous units may help to reduce acne. Furthermore, a deficiency in one or more of these other micronutrients may hinder the ability of taurine and magnesium to perform their functions in the pilosebaceous units. For example, the micronutrient choline is an essential part of phosphatidylcholine, the major phospholipid on the surfaces of lipid droplets. In order for magnesium to be effective in catalyzing the breakdown of lipid droplets to micro-droplets, the micronutrient profile of the lipid droplets should be normal, ensuring functional surface structures on the lipid droplets. Choline deficiency in cells promotes fusion among lipid droplets, leading to lipid droplets that are larger than normal, whereas sufficient phosphatidylcholine appears to help maintain small lipid droplets (Yang et al, 2012). So obtaining adequate dietary or supplemental choline may be therapeutic for acne sufferers in order to help keep the size of lipid droplets in the beneficial range. Furthermore, phosphatidylcholine helps to maintain the round shape of the lipid droplets (Penno et al, 2013); it is plausible that if the sebaceous glands are choline-deficient the shapes of the lipid droplets could be deformed in ways that are more likely to lead to the clogging of the pilosebaceous units. However, choline status can be altered by folate status, because choline and folate share methylation pathways (Jacob et al, 1999). During folate deficiency, choline takes over some of the functions of folate and thereby can become more readily depleted (Sanders and Zeisel, 2007), leading to a decrease in levels of phosphatidylcholine (Jacob et al, 1999), and so a decrease in the phosphatidylcholine available for sebaceous lipid droplets. Thus, choline is a micronutrient that likely affects whether magnesium is successful in its important anti-acne action in the sebaceous glands/ducts.

Certain other micronutrients affect whether taurine is able to perform its anti-acne function in the sebaceous glands. Vitamins D and A, for example, may be critical in ensuring that some taurine in the bloodstream is actually transported across

sebaceous cell membranes by the taurine transporter TauT. The promoter region of the TauT gene has a vitamin D response element, which when activated regulates synthesis of TauT (Chesney and Han, 2013). In order to activate the vitamin D response element, the receptors for vitamin D and retinoic acid (a vitamin A metabolite) in a cell have to be stimulated and form a complex that binds to the vitamin D response element (Chesney and Han, 2013). Such binding to the TauT gene vitamin D response element has been shown to up-regulate TauT synthesis in one normal cell line, from porcine kidney, for example, although it has been shown to down-regulate synthesis in a cancerous cell line, from human breast (Chesney and Han, 2013). In the sebaceous cells, it is likely that activation of the TauT gene vitamin D response element is necessary for TauT synthesis and thus for ensuring adequate taurine levels in the cells. Of note is that vitamin D deficiency in humans has been found to increase urinary excretion of taurine (Chesney et al, 2015), indicating that if adequate vitamin D is not available in the body, then cells cannot adequately utilize the supply of taurine because they cannot access much of it. Vitamin D deficiency is a risk factor for severe acne, and vitamin D supplementation can lessen the severity of lesions (Lim et al, 2016).

Adequate levels of zinc also appear necessary for maintaining adequate levels of taurine: zinc-deficient rats lose more taurine through urine than do normal rats (Hsu, 1977). Zinc is also important in the absorption, transport, and utilization of vitamin A (Christian and West, 1998), a micronutrient that is important along with vitamin D for regulating the taurine transporter. Zinc supplementation has been shown in some studies to reduce acne (Sardana and Garg, 2010), although this effect may be partially immunological. The above examples indicate that deficiencies in certain micronutrients could prevent taurine-magnesium treatment from fully succeeding.

In addition, there appears to be an important circular relationship between taurine, magnesium, and at least one of the supportive micronutrients, vitamin D. Magnesium is an essential cofactor for vitamin D biosynthesis, transport, and activation (Rosanoff et al, 2016). Vitamin D, as described above, is necessary to activate the VDRE of the gene for the main taurine transporter TauT, which enables taurine to be transported into cells. Taurine in its osmolyte role inside cells helps shuttle magnesium ions across cell membranes.

With taurine-magnesium treatment, the fact that many micronutrients are interdependent should be taken into account, along with the recognition that micronutrient deficiencies and insufficiencies are very common in the world, even in the U.S. Vitamin D insufficiency, for example, may be epidemic in the U.S. (Ginde et al, 2009). Furthermore, most micronutrients that are considered to be essential for humans affect some aspect of the proper functioning of skin cells, such as the ability to heal lesions.

Therefore, the acne patient might benefit from, in addition to the taurine-magnesium, a daily multivitamin/mineral supplement, or a subset of micronutrient

supplements, in order to ensure a minimum of micronutrients essential to the basic functioning of the skin, and to prevent a deficiency of a particular micronutrient from interfering with the ability of taurine and magnesium to perform their functions in the skin. The patient could opt to take a multivitamin/mineral supplement or subset of micronutrient supplements tailored to their problem of acne, in addition to but separately from taurine-magnesium. The total amount of magnesium taken in supplements should probably not exceed the RDA, in order to avoid hypermagnesemia and other effects of high magnesium levels, such as the possible enhancement of testosterone (androgen) production (see Cinar et al, 2010). (The magnesium content in standard multivitamin/mineral supplements is generally well below the RDA.) Although taurine at high doses is recommended in this paper for acne, mega-dosing of most vitamins/minerals is not recommended in this paper for acne.

Of note is that high doses of certain micronutrients can very likely exacerbate acne—namely iron, manganese, and (very high) vitamin B-12. The acne patient should probably avoid high levels of these micronutrients for the following reasons:

Iron: Iron is reported to be an absolute requirement for the survival of *Propionibacterium acnes*, the bacterium common in human skin flora that is believed to be one of the causes of acne (Eady et al, 2013). Because iron availability enables so many species of bacteria to thrive, mammals have innate adaptations to sequester iron from bacteria, such as via the iron-binding protein lactoferrin (Weinberg, 2001). Oral lactoferrin tablets have even been shown in one study to reduce the number of acne lesions (Mueller et al, 2011). Iron exposures should preferentially be kept in the normal rather than high range in acne cases.

Manganese: Manganese is one of the few minerals that can replace magnesium in the PKA enzyme (shown in vitro), but when this substitution occurs, the catalytic power of PKA is much lower (Adams, 2001), which interferes with the rapid activation of perilipin A and the breakdown of sebaceous lipid droplets to micro-lipid droplets. Also, as discussed above, manganese stimulates the efflux of taurine out of cells, opposite to magnesium's effect. In addition, as discussed above, manganese catalyzes mTOR, which can lead to activation of the LXR-alpha/SREBP pathways of lipogenesis.

Vitamin B-12: High-dose vitamin B-12 injections or oral therapy can reportedly cause acne that resolves shortly after the therapy is stopped (Veraldi et al, 2017). The link may be that vitamin B-12 contains cobalt. Cobalt, like manganese, is one of the few minerals that can replace magnesium in the PKA enzyme (shown in vitro), but when this substitution occurs, the catalytic power of PKA is much lower (Adams, 2001), which could interfere with the rapid functioning of perilipin A.

Cautionary note on Vitamin B-6: Although sufficient levels Vitamin B-6 are necessary for the body's Vitamin B-6-dependent pathway of internal taurine synthesis, and therefore important for preventing or clearing acne, mega-doses of

Vitamin B-6 according to some informal reports can lead to worse acne. Vitamin B-6 is essential to more than 100 enzymes in the body, not all of which seem to be favorable at grossly increased levels to persons with acne. Caution is suggested because mega-doses of Vitamin B-6 do not just selectively amplify taurine synthesis, but probably other pathways and actions as well.

Early Intervention for Acne Might Stop Acne from Ever Becoming Severe

Probably the most important time to intervene in acne is when it first occurs, which is usually early during the teenage years. If the clogging of the pilosebaceous units can be stopped before it gets serious, it should be much easier to treat. The goal is to stimulate an up-regulation of taurine transporters in the pilosebaceous units and keep ample taurine in the units, along with enough magnesium. An 8-week course of taurine with magnesium at the first onset of acne in teen or pre-teen years, and a 1-2 week course at each hint of future breakout, might be sufficient to keep acne at bay for most teenagers. A long-term prophylactic dose of 500-1000mg/day of taurine with either 200mg/day of magnesium or a multivitamin/mineral containing magnesium might be helpful in preventing most acne breakouts.

Early-in-Life Supplementation with Adequate Taurine Might Help Mitigate Later Acne

Acne in many teenage children might possibly be mitigated if, at much younger ages, the children regularly consume large enough amounts of taurine such that their pilosebaceous units are used to taking up adequate taurine. To ensure that infants and babies receive the dose of taurine that they would get in a natural environment, it is probably best to choose infant formulas that are supplemented with the amount of taurine that is natural in human breast milk.

Taurine Can Come In Different Chemical Conformations, Which May Vary in their Medicinal Usefulness

There are different conformers of taurine. As anti-acne medicines, certain conformers of taurine might work better than others. The biological activity of taurine depends on its specific molecular shape (Cortijo et al, 2009). Taurine is a flexible molecule, as shown especially in the gas phase, where it exhibits 20 different conformers (Cortijo et al, 2009). In more physiologic states of taurine, including the solid state (taurine tablets might be considered an example) and the aqueous state (taurine powder dissolved in water might be considered an example), taurine is a zwitterion that has many fewer conformers. In solid state, taurine assumes a *gauche* conformation (Okaya, 1966; Ohno et al, 1992; Bryant and Jones, 1997), existing as a mixture of *gauche+* and *gauche-* (Song and Kang, 2013). In water, taurine exists in *gauche* and *trans* conformations (Gregoire et al, 1998), and so as a mixture of *gauche+*, *gauche-*, and *trans* (Song and Kang, 2013).

Internally-synthesized taurine, such as that taken from the plasma of individuals who are vegan and do not supplement with taurine, does not appear to have been

analyzed for its conformational spectrum, so it is probably not known yet which mixture of *gauche+*, *gauche-*, and *trans* is most natural for taurine in the bloodstream. It is also not known which conformer of taurine works best as medicine, or which is most readily absorbed when taken orally. In a study of a hypothesized taurine receptor (Frosini et al, 2000), the authors conclude that the preferred taurine conformation at its biological active site results from a *gauche* position. It is possible that there is one single conformer of taurine that fits best with the ligand-binding domain of the LXR-alpha, for the purpose of eliciting a maximal response of inhibiting lipogenesis.

Many companies synthesize taurine for over-the-counter sale to the public, but it is not clear whether all brands of pharmaceutical grade/food grade taurine have essentially the same percentages of each different conformer.

There are Commercial Sources of Taurine that Do Not Seem Best for Sebum Inhibition

There are Dietary Supplements that Pair Magnesium with Taurate for Other Unrelated Medical Disorders

Commercial pills of magnesium taurate—the taurine salt of magnesium—are sold by a number of companies for the purpose of cardiovascular health. Magnesium taurate has been promoted as a possible treatment of stroke, pre-eclampsia, and acute cardiac conditions (McCarty, 1998; 1999). Taurine and magnesium each have numerous different functions and mechanisms-of-action. Their actions for heart health are very different from their actions for controlling sebum volume and flow in the pilosebaceous units. It is not recommended that cardiovascular formulations of magnesium taurate be used for acne. It is not clear, for example, that taurine in a form bound to magnesium, as magnesium taurate, would even bind correctly to the LXR-alpha to function as an inhibitory ligand. The taurine and magnesium recommended in this paper are not bound to each other, but are taken unbound simultaneously in order to trigger in parallel their separate important mechanisms of action.

There are No Studies on Whether the Taurine-Containing “Energy Drinks” Can Decrease Acne

Millions of people around the world drink taurine-containing “energy drinks”, such as the Red Bull and Monster brands. The taurine dose in them is up to 1 g per can. They generally do not contain magnesium. An intake of one energy drink per day would not likely make much if any improvement in acne. The taurine in energy drinks (liquid form) is not necessarily of the same conformation as the taurine in dietary supplement form (solid), which means that it would not necessarily work as well against acne. Furthermore, the taurine in sugary energy drinks might not reach the pilosebaceous units as effectively as taurine supplements do if, for example, the sugar results in some of the taurine being sent to the pancreas to help with insulin

production to regulate blood sugar, instead of being sent to the pilosebaceous units. In addition, some energy drinks contain beta-alanine, which blocks taurine from the taurine transporter; high doses of beta-alanine lead to tissue depletion of taurine, and are regularly used in taurine animal experiments for the purpose of depleting the animal of taurine (Lu and Sturman, 1996). For these and other reasons, it is not recommended that acne patients use energy drinks as their source of supplemental taurine.

Studies on Topical Taurinebromamine Show it has Antimicrobial Properties that Can Reduce Acne

Immunologist and taurine researcher Janusz Marcinkiewicz (not the same researcher as Amy Marcinkiewicz of the micro-lipid droplet experiments) was able to reduce the severity of acne in patients with the topical use of synthetic taurinebromamine, the product of the reaction between taurine and hypobromous acid (J. Marcinkiewicz et al, 2008, abstract; J. Marcinkiewicz, 2009; 2010). In vivo, the immune cells neutrophils and eosinophils naturally generate hypobromous acid as a defense against microbes, and taurine in immune cells scavenges the acid, forming taurinebromamine, which helps prevent excessive inflammation in the body. Taurinebromamine has anti-inflammatory and antimicrobial properties (J. Marcinkiewicz, 2010). In these studies, the researchers topically applied taurinebromamine to the facial skin of patients with mild to moderate acne, reducing lesions by 65% after 6 weeks of treatment. They noted that taurinebromamine was effective at killing *Propionibacterium acnes*. Taurinebromamine is not commercially developed in the U.S. for acne.

The taurinebromamine studies are interesting, but since taurinebromamine is a different molecule from taurine, it is unlikely to be one of the ligands for LXR-alpha that halts lipogenesis.

A Topical Formulation of Taurine with Magnesium Could Be Developed for the Treatment of Acne

Topical taurine-magnesium treatment for acne, developed as a gel or cream, might be even more effective than oral treatment.

Topical taurine at high taurine concentrations has not been used commercially. At low levels it is sometimes present in topical skin products for the purposes of “energizing” the skin, or else as an inactive ingredient.

However, topical preparations of higher-concentration taurine have been developed for experimental purposes. Taurine topically applied to human skin samples has been shown to enter the different layers of dermis (Da Silva et al, 2008).

Topical magnesium salt solutions, oils, and gels have been used historically for a long time for various ailments, including skin conditions. Magnesium ion salts (e.g.,

magnesium chloride) topically applied to human skin samples have been shown in a series of scientific experiments to permeate skin, greatly facilitated by their rapid penetration through hair follicles (Chandrasekaran et al, 2016). This follicular route for delivery of an acne formulation might be ideal. According to Schaefer et al (1982), in the initial minutes after application of a solution to skin, shunt diffusion—permeation via pilosebaceous units—can be much greater than bulk diffusion—permeation via stratum corneum. Topical magnesium ions in formulation could potentially reach the sebaceous glands via 3 ways: 1) by penetrating the hair follicles as far as their attached sebaceous ducts and then travelling through these ducts to the sebaceous glands; 2) by diffusing through the walls of the hair follicles to the circulatory system and eventually circulating to the sebaceous glands; 3) by diffusing through the stratum corneum to the dermis. As Chandrasekaran et al (2014) further suggest, in commercial formulations the addition of pharmaceutical penetration enhancers might greatly enhance the diffusion of magnesium ions through skin under normal physiological conditions.

Importantly, both topical taurine and topical magnesium may be beneficial for skin in ways that make them unlikely to cause detrimental side-effects in a commercial formulation: both these micronutrients hydrate the skin. Taurine does so in its role as an osmolyte (Janeke et al, 2003). Magnesium has been shown in an experiment by Chandrasekaran (2016) to increase skin hydration by almost 2 folds within the first 6 hours after treatment.

Topical taurine-magnesium treatment could be used in conjunction with oral taurine-magnesium treatment for difficult or severe cases of acne, simultaneously delivering these micronutrients from the inside-out and the outside-in. (Note: If one conformer of taurine is found to be more effective than the others in binding to LXR-alpha, then the topical gel should be prepared in a way that favors that conformer.)

Taurine-Magnesium Treatment for Types of Acne Other Than *Vulgaris* Could Also Be Investigated

It is not known if “acne” rosacea—a facial skin disease that involves the sebaceous area and that is common in older people—is related to acne *vulgaris*. But as with acne *vulgaris*, the sebum profile of patients with rosacea can be different from normal (Ni Raghallaigh et al, 2012). If high-dose taurine with low-dose magnesium is shown to be clinically successful for treating acne *vulgaris*, it could be tried for acne *rosacea*, and for other types of acne.

There are Some Miscellaneous Considerations in Using High-Dose Taurine for Acne

To Have a Surplus of Taurine in the Bloodstream, High Doses of Supplementary Taurine May Be Necessary, Even Though Much of It Will Be Urinated Out

The fact that some taurine from a patient is excreted through urine does not indicate that sufficient taurine is already available in the bloodstream for delivery to the pilosebaceous units. In order to raise tissue levels of some micronutrients, such as taurine, large supplementary doses may need to be given, even to the extent that large amounts end up being excreted through urine. The renal system does use a significant amount of taurine anyway (Chesney et al, 2010). Although most of the taurine that reaches the kidneys can be reabsorbed instead of excreted (Chesney et al, 2010), much taurine is excreted in urine when serum taurine levels are fairly high, such as with a diet high in seafood (Yamori et al, 2001). Nevertheless, a high dose of taurine, rather than a low dose, is what is therapeutic for active acne (when taken with magnesium). Increasing the supplemental taurine dose by another full gram, for example, can make a huge difference in whether the acne clears, as seen with some of the volunteers.

Until Further Information, Three Restrictions Should Be Mentioned Regarding Oral High-Dose Taurine Supplementation

Pregnancy/Lactation: Taurine is not teratogenic, and in fact it is essential for embryonic and fetal development. However, until further animal and human studies are done it may be prudent to avoid exposing the embryo, fetus, and neonate to greatly excess taurine levels. Studies in animals show that, although perinatal taurine depletion has many adverse effects, perinatal excess taurine supplementation also can be associated later in life with modest adverse effects, such as increased arterial pressure and altered renal parameters (Roysommuti et al, 2009; Roysommuti et al, 2010; Roysommuti and Wyss, 2014). Pregnant and lactating women with acne may not qualify for oral high-dose taurine treatment (greater than 500mg/day). Topical taurine treatment might be safer for them.

2-Drink Per Day Alcohol Limit: There were only 2 slight restrictions that I requested of the volunteers regarding their diets or lifestyles during treatment. The first was that for the duration of their treatments they limit their alcohol consumption to 2 alcoholic drinks per day. The reason for this request was precautionary, in response to articles claiming that a couple of mysterious deaths in Europe had occurred in persons who had consumed multiple alcoholic drinks mixed with “energy drinks” containing high levels of caffeine and many other ingredients, including taurine. There are no known dangers from taurine. This slight restriction on alcohol intake suggested for persons on full taurine-magnesium treatment contrasts sharply with the extreme restriction on alcohol intake mandated for acne patients on isotretinoin treatment.

No Taurine-Containing Energy Drinks During Taurine-Magnesium Treatment: The second slight dietary restriction for volunteers was that they refrain from drinking taurine-containing energy drinks during taurine-magnesium treatment. It seems prudent not to increase the total taurine dose beyond the treatment dose.

PART VII: SUMMARY

Experiments Could Be Performed to Better Understand the Extent of the Anti-Acne Functions of Taurine and Magnesium in the Pilosebaceous Unit

Experiments that could lead to an understanding of the relationship between taurine and acne prevention include the following: (1) An experiment paralleling that of Hoang et al (2012)—which found that taurine is a lipogenesis-halting ligand of the LXR-alpha in liver cells—to see if taurine has exactly the same effects on the LXR-alpha of sebaceous cells. (2) An analysis of the sebum of individuals taking high-dose taurine supplements to see if taurine shows up in the sebum, and if so, whether the taurine reduces the viscosity of sebum. (3) Measurements of the density of taurine transporters TauT and PAT1 in the pilosebaceous units of skin samples of taurine-supplemented animals and humans to better understand the system of taurine entry into pilosebaceous cells. (4) An analysis of the different conformations of taurine to find out which conformation binds best to the LXR-alpha for acne prevention, followed by an analysis of which conformations are in taurine tablets/capsules vs taurine powder-stirred-into-water.

Experiments that could lead to an understanding of the relationship between magnesium and acne prevention include the following: (1) An experiment paralleling that of A. Marcinkiewicz et al (2006)—which found that protein kinase A phosphorylation of perilipin A breaks down lipid droplets in adipose cells—to see if protein kinase A phosphorylation of perilipin A has exactly the same cascade of effects in sebaceous cells and sebaceous ducts. (2) An analysis of the sebum of individuals taking magnesium supplements to see if magnesium shows up in the sebum, and if so, whether the magnesium reduces the viscosity of sebum.

Studies Could Be Done to Analyze Whether Early-in-Life Taurine Deficiency is a Risk Factor for Later Acne

It might be helpful to know whether taurine intake early in life correlates negatively with acne severity during teen years. Early-in-life taurine intake by an individual could be estimated from estimates of the mother's intake of meat/fish during pregnancy and lactation, duration of breast-feeding, quantity of taurine in the particular infant formula the individual was fed as a baby, quantity of meat/fish intake of baby-food or other food during the first couple of years, and type and quantity of animal milk the individual was fed as a baby. It also might be helpful to know whether the severity of acne in teens has decreased generally since taurine was added to most infant formulas, controlling for factors such as glycemic load.

There May Be Additional Minor Dietary Factors Influencing Acne

Dietary factors influencing acne are not necessarily completely accounted for by the above understanding of the etiology of acne. Some studies have found an inconsistent link between diet and acne (for reviews on diet and acne see Veith and

Silverberg, 2011; Spencer et al, 2009). Many people find that there are particular foods in their diet that flare up their acne, but lists of such foods seem idiosyncratic. For example, different people might point to chocolate, or soy oil, or nuts, or butter, or cinnamon, as acne-causing, whereas other people might find that these foods have no effect on their acne. There is no known general explanation as to why idiosyncratic relationships between foods and acne occur, but the reasons for the association between acne and certain foods in some people may come to light on a case-by-case basis.

For example, chocolate is an extremely popular food shown in some but not all studies on the chocolate-acne connection to be an inducer of acne (Delost, 2016; Caperton et al, 2014). Chocolate is often contaminated by cadmium, a toxic metal with no known biological role, because the cacao plant readily takes up natural cadmium from soil, especially in volcanic regions, as well as industrial cadmium in soil, from, for example, certain fertilizers (Chavez et al, 2015). The root of the cacao plant absorbs cadmium via transporters intended for nutrient metals (Pereira de Araujo et al, 2017). The different brands and types of chocolate/cocoa can exhibit very different cadmium concentrations (Villa et al, 2014; ConsumerLabs, 2017), since different cacao clones in the same growing region accumulate cadmium at different rates, and different soil regions have different cadmium levels (Arevalo-Gardini et al, 2017). Cadmium levels in blood have been found, in a study of acne in Nigeria, to be strongly correlated with acne severity, such that as individuals were grouped according to acne severity—from zero to mild to moderate to severe—the average blood levels of cadmium in each group increased by a factor of 3 (Ikaraoa et al, 2017). An explanation for the link between cadmium and acne is that cadmium, like manganese and cobalt, is one of the 3 metals that can replace magnesium in the PKA enzyme; when such cadmium substitution occurs, however, the catalytic power of PKA is much lower (Adams, 2001), which could interfere with the rapid functioning of perilipin A in triggering the breakdown of lipid droplets.

If an individual's taurine and magnesium intake become optimal with supplementation, the influence of particular foods on acne is likely to wane. Regarding the case of chocolate, taurine has the additional benefit of reducing cadmium bioavailability/toxicity by increasing the rate that the body excretes cadmium (Hwang and Wang, 2001).

Summary of Research Paper

High-dose taurine supplementation combined with low-dose magnesium supplementation happens to be very effective against acne in the individuals tested so far. The basic premise of this research paper is that the natural design of the pilosebaceous units has built-in ways to prevent the clogging of these units, incorporating the special use of taurine and magnesium. Understanding how healthy pilosebaceous units naturally prevent acne entails looking at the system of sebum production, regulation, and flow and answering at minimum the following 2 questions: 1) How do the pilosebaceous units halt lipogenesis in the sebaceous

glands to prevent runaway oil production? and 2) How do the pilosebaceous units ensure the well-timed breakdown of the large lipid droplets into micro-droplets and usable lipid constituents to prevent excessive lipid droplet size? An answer to question 1 is “taurine” and to question 2 “magnesium”.

The natural anti-acne mechanisms of action in the pilosebaceous units become disrupted in individuals of most agricultural societies. A major reason appears to be that the diets are way too low in taurine and often too low in magnesium to counter the normal amount of lipogenesis that occurs in response to androgens, and especially to counter the abnormal amount of lipogenesis that can occur in response to evolutionarily-novel dietary factors that directly or indirectly stimulate lipogenesis, such as high glycemic load and cow’s milk. The result is often acne.

To reverse the course of acne, a surplus of taurine along with adequate magnesium may be necessary. With taurine-magnesium supplementation, a signal to convey to the body is that ample taurine and magnesium are available in the environment and so the adequate distribution of taurine and magnesium to all the tissues should be allowed, including to those tissues of secondary importance, such as the pilosebaceous units. The best strategy for treating acne is at its onset, before it becomes serious or chronic. Treating early-in-life taurine insufficiency might even be a strategy to help prevent or mitigate later teenage acne.

Supplementing the skin with high-dose taurine with low-dose magnesium may be the way to simply amplify nature’s original way of preventing acne.

PART VIII: REFERENCES

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