

Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine

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Abstract

Acne vulgaris has long been postulated to feature a gastrointestinal mechanism, dating back 80 years to dermatologists John H. Stokes and Donald M. Pillsbury. They hypothesised that emotional states (e.g. depression and anxiety) could alter normal intestinal microbiota, increase intestinal permeability, and contribute to systemic inflammation. They were also among the first to propose the use of probiotic *Lactobacillus acidophilus* cultures. In recent years, aspects of this gut-brain-skin theory have been further validated via modern scientific investigations. It is evident that gut microbes and oral probiotics could be linked to the skin, and particularly acne severity, by their ability to influence systemic inflammation, oxidative stress, glycaemic control, tissue lipid content, and even mood. This intricate relationship between gut microbiota and the skin may also be influenced by diet, a current area of intense scrutiny by those who study acne. Here we provide a historical background to the gut-brain-skin theory in acne, followed by a summary of contemporary investigations and clinical implications.

Keywords: acne, probiotics, gastrointestinal tract, gut, brain, skin, diet, microbiota, depression, anxiety

1. Introduction

Acne vulgaris is a common disease in developed nations, one that has increased in frequency in the last half century, particularly among adult women (Silverberg and Weinberg, 2001). In general terms, acne is characterised by sebum overproduction, follicular hyperkeratinisation, and an increased release of inflammatory-mediating chemicals. Along with androgens and other pathogenic influences, microbes are also at work in the development of acne (Kurokawa *et al.*, 2009; Strauss *et al.*, 2007). In the treatment of acne, one of the prevailing tenets has revolved around the eradication of a bacterium known as *Propionibacterium acnes*. The use of oral and topical antibiotics, often in combination, has been a mainstay of acne therapy for decades, providing relief for millions of acne sufferers. However, with the recent emergence of bacterial resistance, this historical first-line treatment has become less and less effective (Bowe and Logan, 2010; Patel *et al.*, 2010). As such,

the search for a safe and effective alternative to previously potent antibiotic therapy remains vigorous. In this quest, dermatological scientists have turned their attention to the potential value of probiotic organisms. Rather than non-specific chemical destruction of *P. acnes*, with its far reaching effects on the human microbiome, investigators are exploring the possibility of utilising non-pathogenic bacteria to improve the skin, with collateral benefits to the gastrointestinal tract and the psyche as well.

It has long been recognised that chronic skin conditions and mental health disorders are often co-morbid, and in recent years specialty neurodermatology and psychodermatology groups have emerged. Acne vulgaris is frequently associated with depression, anxiety, and other psychological ailments. Accordingly, mental health impairment scores are higher among acne patients compared to a number of other chronic, non-psychiatric medical conditions such as epilepsy and diabetes (Loney *et al.*, 2008; Magin *et al.*,

2006; Mallon *et al.*, 1999; Purvis *et al.*, 2006; Rapp *et al.*, 2004; Thomas, 2004; Uhlenhake *et al.*, 2010). In addition to the psychological fallout, there exist indications that acne patients are at a higher risk for gastrointestinal distress. For example, an investigation of over 13,000 adolescents showed that those with acne were more likely to experience gastrointestinal symptoms including constipation, halitosis, and gastric reflux. More specifically, abdominal bloating was 37% more likely to be associated with acne and other seborrheic diseases (Zhang *et al.*, 2008).

The link between dermatology and mental health is being further understood by rising evidence that the functional integrity and microbial residents of the intestinal tract may play a mediating role in both skin inflammation and emotional behaviour. The physiological link between intestinal microbiota, psychological symptoms such as depression, and inflammatory skin conditions such as acne has long been examined. Here we review the 80-year-old gut-brain-skin unifying theory, first postulated in 1930 by dermatologists John H. Stokes and Donald M. Pillsbury (Stokes and Pillsbury, 1930), and provide a historical perspective to the contemporary investigations and clinical implications of the gut-brain-skin connection in acne.

2. The gut-brain-skin theory

Stokes and Pillsbury (1930) utilised various lines of experimental evidence and clinical anecdotes to provide a 'theoretical and practical consideration of a gastrointestinal mechanism' to explain how the skin is influenced by emotional and nervous states. The authors attributed emotional states such as depression, worry and anxiety to altered gastrointestinal tract function and microbiota, which they theorised, in turn promotes local and systemic inflammation. They offered, as they said, an important linkage between emotional states and inflammatory skin conditions 'by way of the physiology and bacteriology of the gastrointestinal tract'. Based on evidence that as many as 40% of acne patients have hypochlorhydria, Stokes and Pillsbury hypothesised that insufficient stomach acid may induce the migration of colonic bacteria towards distal portions of the small intestine, and also disrupt the normal intestinal microflora. Furthermore, the authors suggested that stress-induced alterations to microbial flora could increase intestinal permeability, thus setting the stage for systemic and local skin inflammation. Stokes and Pillsbury recommended the 'direct introduction of acidophil organisms in cultures such as those of *Bacillus acidophilus*' to terminate this stress-induced cycle. They also advocated for an acidophilus milk preparation and cod liver oil, well before their current classification as probiotics and a rich source of omega-3 fatty acids, respectively. Prior to Stokes' and Pillsbury's gut-brain-skin 'emotional linkage' theory, some physicians had previously reported low stool levels of *Lactobacillus acidophilus* in patients with a variety of

mental health disorders, as well as mental health benefits from the oral administration of lactic acid bacilli tablets and *Lactobacillus*-fermented drinks (Norman, 1909; Phillips, 1910; Shera, 1930).

The work of Stokes and Pillsbury lay dormant and unreferenced for eight decades, removed from the archives only recently (Bowe and Logan, 2011). Its historical disappearance was almost certainly because it was published precisely at a time when researchers and clinicians were turning away from the 'auto-intoxication' and 'intestinal toxemia' theories that once dominated medical thinking in the early 20th century. The central tenet of intestinal toxemia was that gut-derived microbes and/or microbial breakdown products (e.g. putrefactive substances) may play a role in systemic health, skin conditions and mental health in particular. The broad sentiment was captured by gastroenterologist Milton H. Mack (Mack, 1911) writing in the 'Illinois Medical Journal' on the topic of intestinal toxemia – 'Acne and eczema are both traceable to this fountainhead of diseases ... if in a case of urticaria we look to the intestinal tract, why not in eczema and acne?' In 1917, in their monthly 'Etiology and Diagnosis' section ((Editors., 1917), the editors of 'American Medicine' linked acne to intestinal toxemia in some cases, stating that 'the activating factors are in a certain percentage of cases either the colon bacillus, or its toxins, or both'. Although there was some research indicating legitimacy to certain aspects of the concept, from the early 1900s to the early 1930s, intestinal toxemia became a Petri dish of pseudoscientific claims, charlatan sales of so-called colon cleansers, and unproven suggestions that auto-intoxication was at the root of all chronic medical conditions (Ernst, 1997). At the extreme, it was suggested in an article entitled 'Dermatological Aspects of Chronic Intestinal Stasis' (1917), that acne might be treated by intestinal surgery (Cunningham, 1917). Some of the more important preliminary studies during this period, those showing a potential role for intestinal permeability, carbohydrate intolerance and intestinal bacterial overgrowth, as the pathways for what were otherwise being blanket-labelled as intestinal toxemia, were never followed up (Adami, 1914; Jankelson, 1922; Johnson and Goodall, 1904; Turck, 1918). The more rational ideas of the period, including the suggestion to examine the influence of commensal endotoxin production as a potential factor in intestinal toxemia (Andrewes, 1913), were obscured by outlandish marketing claims and the voices of a few who found auto-intoxication at every clinical turn (i.e. that it was a fountainhead).

3. Contemporary evidence

Hypochlorhydria has been confirmed in recent years to be a significant risk factor for small intestinal bacterial overgrowth (SIBO). In fact, SIBO is detected in half of patients on long-term proton pump inhibitor treatment

via hydrogen breath testing (Lombardo *et al.*, 2010). The presentation of SIBO exhibits a wide range, from being asymptomatic to its extreme as a severe malabsorption syndrome. Many patients experience very mild gastrointestinal symptoms, including bloating, diarrhoea, abdominal pain, and constipation (Bures *et al.*, 2010). Reports also show that SIBO is prevalent in functional syndromes including fibromyalgia and chronic fatigue syndrome (Goebel *et al.*, 2008). Although the frequency of SIBO in functional gastrointestinal disorders remains a matter of debate, largely because its presence has been based upon breath testing with questionable sensitivity and specificity, newer culture-based investigations are providing validation (Pylaris, *et al.* 2012). Due to bacterial interference, SIBO can compromise proper absorption of carbohydrates, proteins, fats, B vitamins, and other micronutrients. The overgrowth of bacteria can produce toxic metabolites, compete for nutrients successfully, and cause direct injury to small intestinal enterocytes (Toskes, 1993). In accordance with the supposition of Stokes and Pillsbury (1930), SIBO has recently been associated with increased intestinal permeability, whereas correction of SIBO by antimicrobial treatment helps to restore the normal intestinal barrier (Lauritano *et al.*, 2010). Experimental studies show that psychological stress encourages bacterial overgrowth, stagnates normal small intestinal transit time, and compromises the intestinal barrier (Wang and Wu, 2005). Multiple studies show that hypochlorhydria is common in states of depression and SIBO is strongly associated with anxiety and depression, while eradication of SIBO improves emotional symptoms (Addolorato *et al.*, 2008; Pimentel *et al.*, 2000). Although the frequency of SIBO in acne vulgaris has yet to be examined, a recent study reports that SIBO is 10 times more prevalent in those with acne rosacea vs. healthy controls. The rosacea patients see marked clinical improvement upon resolution of SIBO (Parodi *et al.*, 2008). Probiotic oral administration has also proven beneficial in the reduction of SIBO (Barrett *et al.*, 2008). Interestingly, the omega-3 fatty acid-rich cod liver oil recommended by Stokes and Pillsbury (1930) may have been ahead of its scientific time. Not only does a diet lacking omega-3 increase SIBO (Ralph *et al.*, 2004), but it has also been linked repeatedly to an increased risk of depressive symptoms (Freeman, 2009). A small series of case reports specify the value of omega-3 fatty acids in both the clinical grade of acne and global aspects of well-being (Rubin *et al.*, 2008).

There have been hints that intestinal permeability may be amplified in acne vulgaris. Acne patients were more likely to show enhanced reactivity to stool-isolated bacterial strains in an older study that used a blood serum complement fixation test. Of the 57 patients with acne, approximately 66% showed positive reactivity to stool-isolated coliforms, compared to none of the control patients without active skin disease (Strickler *et al.*, 1916). Furthermore, acne patients

showed both the presence of and high reactivity to blood lipopolysaccharide (LPS) endotoxins as measured by the stellate fibrin crystal test. In the study of 40 acne patients, 65% of the acne patients showed a positive reaction, whereas none of the matched healthy controls reacted to the *Escherichia coli* lipopolysaccharide endotoxin (*E. coli* LPS) (Juhlin and Michaelsson, 1983). These results suggest that gut microbes may enhance the presence of circulating endotoxins in acne vulgaris patients, indicating that intestinal permeability is a potential issue for many acne patients. Since enhanced reactivity to *E. coli* LPS is observed in irritable bowel patients with higher anxiety levels (Viana *et al.*, 2010), and systemic *E. coli* LPS itself can produce depression-like behaviour in animals (Liebregts *et al.*, 2007), an updated investigation of the endotoxin's role in acne seems warranted.

Currently, it is unknown if constipation is more prevalent in those with acne, as confidently suspected by Stokes and many of his contemporaries. They had claimed constipation was an 'important factor' (Gibbes, 1912) and even 'the rule' rather than the exception (Cleveland, 1928). One older study using a bismuth test beverage and objective fluoroscopy reported intestinal stagnation in 47% of 30 acne patients, as well as constipation as a clinical complaint in 40% of the patients (Ketrion and King, 1916). Although a recent population study involving 13,000 adolescents indicates that constipation is more frequent in acne patients (Zhang *et al.*, 2008), it is tempting to dismiss the finding as having no relevance whatsoever to the pathogenesis of acne and/or depression. However, an important study from 2005 provides cause for further consideration; faecal concentrations of *Lactobacillus* and *Bifidobacterium* were significantly lower and intestinal permeability was significantly higher among 57 patients with functional constipation vs. healthy adults without constipation. In addition, the study noted an enhanced systemic immune response, almost certainly due to larger molecules distributing across the intestinal barrier (Khalif *et al.*, 2005). Another recent study shows that chronic constipation, in otherwise healthy adults without irritable bowel syndrome, is associated with significant alterations to the intestinal microflora (Attaluri *et al.*, 2010). Combined with new findings of increased gut permeability in depressed patients (Maes *et al.*, 2008), we must surely re-examine the obvious overlap between constipation and depression (Hillila *et al.*, 2008), and the more specific finding of longer whole gut transit time positively correlated with depression (Gorard *et al.*, 1996).

4. Intestinal microflora

The Stokes-Pillsbury theory was predicated upon changes to both the residential location of gut microbes as well as the quantity of microbes in the intestinal tract. This suggestion has also been supported by contemporary investigations.

Experimental and human studies have shown that a variety of physiological and psychological stressors – crowding, confinement, extremes of temperature, acoustics, and academic examination – can disrupt normal intestinal microflora (Knowles *et al.*, 2008; Logan and Katzman, 2005; Logan *et al.*, 2003). Most remarkable among these stress-induced changes are reductions in lactobacilli and bifidobacteria species.

Unfortunately, the potential of stress-induced alterations to the gastrointestinal microflora in acne patients has received little attention. The first attempt to examine the intestinal bacterial microflora took place in a 1955 investigation of 10 acne patients. While the small sample group does not allow for generalisations to be made, the authors did conclude there were no major differences in a small subset of potentially pathogenic bacteria in acne patients vs. controls using culture technique (Loveman *et al.*, 1955). Interestingly, we find it note-worthy that *Bacteroides* spp. were more commonly isolated from the acne patients, particularly since elevations of *Bacteroides* have been noted in humans under psychological stress (Holdeman *et al.*, 1976). Unfortunately, this early pilot study was restricted to a small set of bacterial genera and did not culture for potentially beneficial bacteria whose role in acne we are now questioning, such as lactobacilli and *Bifidobacterium*. Aside from this pilot study, the only other investigations examining the intestinal microflora in acne, to our knowledge, are within non-English language journals. A Chinese study of patients with seborrheic dermatitis reported disruptions of the normal gastrointestinal microflora (Zhang *et al.*, 1999), while Russian investigators noted that 54% of acne patients have marked alterations to the intestinal microflora (Volkova *et al.*, 2001). As the molecular identification of intestinal microbial inhabitants has recently advanced, we are hopeful that investigators will find a renewed interest in the potential changes to the enteric microbial profile among acne patients.

5. Probiotic administration

The bacteria *L. acidophilus* and *L. acidophilus*-fermented milk products were frequently recommended by Stokes and Pillsbury (1930) as a treatment modality in the context of the gut-brain-skin inflammatory process. In addition, *L. acidophilus* cultures were mentioned by other physicians in the 1930s as a popular internal means to treat acne (Ereaux, 1938). In spite of the apparent appeal of what would later be described as probiotics, there was little research to determine efficacy. It was not until 1961 that the first formal clinical case series on the potential value of *Lactobacillus* probiotics was published. Robert H. Siver, a physician from Union Memorial Hospital in Baltimore, followed 300 patients who were administered a commercially available probiotic (Lactinex tablets providing a mixture of *L. acidophilus* and *Lactobacillus bulgaricus*). The protocol

he employed included probiotic supplementation for 8 days, followed by two-week wash out, and then re-introduction for eight more days. The rationale for this dosing regimen is unclear. Regardless, he documented that 80% of acne patients had some degree of clinical improvement, and that the probiotic tablets were most effective in cases of inflammatory acne. Lacking a placebo control, Dr. Siver merely concluded that ‘interactions of skin manifestations of acne vulgaris and of metabolic processes of the intestinal tract are suggestive’ (Siver, 1961).

Subsequent studies of the internal application of probiotic supplements in acne have been restricted to non-English language journals. The first was an Italian study involving 40 patients; half were administered an oral supplement of 250 mg freeze-dried *L. acidophilus* and *Bifidobacterium bifidum* as an adjuvant to standard care. Not only did the probiotic-supplemented group show better clinical outcomes, but the group displayed better tolerance and compliance with antibiotics (Marchetti *et al.*, 1987). An investigation from Russia also supports the benefit of probiotics added to standard care, reporting faster achievement of significant clinical improvement in those who received probiotics (Volkova *et al.*, 2001). These foreign investigations are difficult to critically evaluate, and for now should serve simply as a further indication that oral probiotics deserve further investigation in acne vulgaris. Meanwhile, a recent investigation of 56 acne patients established that consumption of a *Lactobacillus*-fermented dairy beverage improved the clinical grade of acne over 12 weeks. Specifically, the probiotic drink effectively reduced the total lesion count in association with a marked reduction in sebum production. While the addition of lactoferrin (an anti-inflammatory milk protein) to the probiotic beverage increased the efficacy of inflammatory lesion reduction, the benefits observed by unaccompanied probiotic drink consumption lend further support to the notion that probiotics have an adjuvant role to play in acne therapy (Kim *et al.*, 2010).

Other potential therapeutic pathways provide theoretical support for the administration of oral probiotics as adjuvant care in acne vulgaris. Recent studies have shown that orally consumed pre- and probiotics can reduce systemic markers of oxidative stress and inflammation (Mikelsaar and Zilmer, 2009; Naruszewicz *et al.*, 2002; Schiffrin *et al.*, 2007). Because acne patients experience a local burden of lipid peroxidation and thus maintain a great demand upon blood-derived antioxidants (Bowe *et al.*, 2012), the ability of oral probiotics to control systemic oxidative stress (Fu *et al.*, 2010) may surely be an important therapeutic pathway. In a one-month study, the administration of *Lactobacillus rhamnosus* IMC 501 and *Lactobacillus paracasei* IMC 502 minimised the systemic oxidative stress, lipid peroxidation in particular, associated with intense physical activity (Martarelli *et al.*, 2011). Oral

probiotics can regulate inflammatory cytokine release within the skin (Hacini-Rachinel *et al.*, 2009), and a specific reduction in interleukin-1 alpha (IL-1 α) noted under certain experimental conditions (Cazzola *et al.*, 2010) would certainly be of potential benefit in acne. In accordance with the observations seen after internal antibiotic use, oral encapsulated probiotics also have the potential to change the microbial profile at sites far removed from the gastrointestinal tract (Gluck and Gebbers, 2003). Below we will address the potential of probiotics to mediate acne through the gut-brain connection.

6. Topical probiotics

Although this review is intended to focus on the gut-brain-skin connection, the ability of oral probiotics to affect changes in distant microbial residents suggests that topical probiotics are worthy of brief discussion. Once again, the idea that topically applied probiotics may be useful in acne vulgaris is not a new one. The first report investigating 'topical bacteriotherapy' was published in 1912, and it concluded that local *L. bulgaricus* may be helpful in acne and seborrhoea (Peyri, 1912). However, it was not until 1999 that the potential skin-specific benefits of lactic acid bacterial application were investigated with proper scientific technique. Specifically, researchers demonstrated that the lactic acid bacteria *Streptococcus thermophilus*, a species found in most yogurts, may increase ceramide production when applied to the skin as a cream for 7 days (Di Marzio *et al.*, 1999). This work has since been replicated (Di Marzio *et al.*, 2003; Di Marzio *et al.*, 2008) and is relevant to acne because some ceramide sphingolipids, most notably phytosphingosine (PS), provide both antimicrobial activity against *P. acnes* and direct anti-inflammatory activity (Pavicic *et al.*, 2007). Sphingolipids have previously been reported to be low in acne (Yamamoto *et al.*, 1995); indeed, the seasonal loss of ceramides in the winter months may be a catalyst for the higher occurrence of dermatological office visits for acne in that season (Hancox *et al.*, 2004). Moreover, a recent 2-month pilot study showed that topical application of 0.2% PS reduced papules and pustules by 89% (Pavicic *et al.*, 2007).

Additional research demonstrating the potential value of topical probiotics include reports that *Bifidobacterium longum* strains can attenuate skin inflammation mediated by substance P (Gueniché *et al.*, 2010a,b). The role of substance P in this probiotic-induced anti-inflammatory process is noteworthy, because substance P may be a primary mediator of stress-induced amplification of inflammation and sebum production in acne (Lee *et al.*, 2008). Additionally, two separate studies have shown that various probiotic lactic acid bacteria can provide *in vitro* antimicrobial activity against *P. acnes* (Al-Ghazzewi and Tester, 2010; Kang *et al.*, 2009). The latter study by Kang *et al.* (2009) also included a clinical arm which indicated that topical *Enterococcus*

faecalis probiotic lotion application reduced inflammatory lesions by over 50% vs. placebo in 8 weeks.

P. acnes growth has been shown to be inhibited by certain bacteria-secreted substances, such as antimicrobial peptides and organic acids from various bacterial strains. For example, the *in vitro* inhibition of *P. acnes* by human-derived *Lactobacillus reuteri* strains was attributed to its organic acid production (Kang *et al.*, 2012). On the other hand, *Streptococcus salivarius*, a prominent oral microbe in healthy humans, secretes a bacteriocin-like inhibitory substance (BLIS-like substance) capable of hindering *P. acnes* growth (Bowe *et al.*, 2006). In addition to the BLIS-like substance's antimicrobial activity, the *S. salivarius* bacterial cells themselves inhibit a number of inflammatory pathways, thus serving as immune modulators (Cosseau *et al.*, 2008). A recent *in vitro* study has also shown that *Bifidobacterium* strains, isolated from stool samples of healthy donors, can inhibit the growth of *P. acnes*. In particular, *Bifidobacterium adolescentis* SPM0308 and *B. longum* SPM1207 reduced the viability of *P. acnes* by 84% and 75% respectively (Lee *et al.*, 2012). Finally, the application of select bacteria to the skin may behave as a protective shield, similar to a physical barrier. This so-called bacterial interference is thought to prevent colonisation by other potentially pathogenic strains through competitive inhibition of binding sites (Brook, 1999).

7. Internal bacteriotherapy and the gut-brain-skin triangle

As stated, there have been older commentaries and clinical anecdotes that suggest there may be benefits to oral consumption of lactic acid bacteria in alleviating depressive symptoms. Patients with mental health disorders were reported to have very low levels of *L. acidophilus*. In 1924, a series of physician case reports indicated value of oral *L. acidophilus* in the treatment of both acne and mental health disorders. In addition to observed improvements in complexion due to *L. acidophilus*, it was stated that 'in certain patients it even seemingly contributes to mental improvement' (Saunders, 1924). It was also noted that oral consumption of the yeast *Saccharomyces cerevisiae* could improve both constipation and acne vulgaris (Hawk *et al.*, 1917). This proves to be an interesting anecdote when considering new research on the ability of the yeast to improve the integrity of an unstable gut barrier (Generoso *et al.*, 2010). However, many of these early reports were explained too simply by the ability of oral lactic acid bacteria to improve bowel function and reduce constipation. During early 20th century, clinicians too often associated constipation with the root of all acne and depression. Furthermore, these clinical case reports were never advanced to proper scientific investigations.

The first scientific proposal that probiotics might influence states of human fatigue and depressive disorders (Logan and Katzman, 2005; Logan *et al.*, 2003) provided a number of different mechanistic pathways for future scientific exploration. Subsequently, the effects of intentional manipulation of the intestinal flora on mental health have finally been explored. These studies have examined the potential physiological mechanisms of action due to gut microbial changes. The first investigation noted that oral administration of probiotics via laboratory chow appears to increase peripheral tryptophan levels, and also alter dopamine and serotonin turnover in the frontal cortex and limbic system (Desbonnet *et al.*, 2008). Indeed, oral probiotics have been shown to increase nerve cell resiliency and reduce apoptosis during conditions of experimental physiological stress (Girard *et al.*, 2009). Probiotic-fortified laboratory chow increases the tissue levels of omega-3 fatty acids, leading to normal mood states (Wall *et al.*, 2010). Meanwhile, in humans the plasma levels of anti-inflammatory fatty acids such as gamma-linolenic acid (GLA) increase when they are co-administered with probiotics (Puch *et al.*, 2008). Non-pathogenic bifidobacteria presence in the gastrointestinal tract appears to attenuate an exaggerated stress response and maintain adequate levels of brain derived neurotrophic factor (BDNF), a neuropeptide known to be low in depression (Sudo *et al.*, 2004). Alternatively, even mild chronic inflammation of the gastrointestinal tract can provoke anxiety and diminish BDNF production in animals (Bercik *et al.*, 2010). It was recently reported that oral bifidobacteria provide both systemic protection against lipid peroxidation and decreases brain monoamine oxidase activity, thereby potentially increasing inter-synaptic neurotransmitter levels (Shen *et al.*, 2011). Further studies using experimental models of psychological stress demonstrate that oral bifidobacteria reduce systemic inflammatory cytokines and normalise stress hormones in the brains of rats. Intentional dietary manipulation that doubles the faecal *Lactobacillus* totals in animals results in decreased anxiety-like behaviour (Desbonnet *et al.*, 2010; Li *et al.*, 2009).

Studies involving mice reared in germ-free environments and consuming only autoclaved food indicate that such animals display the human equivalent of what might be decreased anxiety vs. animals raised with an intact intestinal microbiota (one without specific pathogens). Remarkably, these behavioural changes have been associated with differences in neurotransmitter turnover, as well as genetic and protein expression for receptors and neuronal plasticity (Diaz Heijtz *et al.*, 2011). For example, germ-free mice were noted to have decreased *N*-methyl-D-aspartate (NMDA) receptor mRNA expression in the central amygdala, suggesting decreased amygdala activity in concert with decreased behavioural signs of anxiety (Diaz Heijtz *et al.*, 2011). Of course, it is also possible that germ-free mice with potentially reduced amygdala activity may be high-

risk takers; therefore, the clinical relevance of studies with germ-free mice is unknown. Research involving a strain of *L. rhamnosus* indicates that its administration to healthy animals under stress reduces anxiety and depression-like behaviours in experimental models such as the elevated plus maze and forced swim tests. The behavioural changes were linked to differential alterations in the gamma-aminobutyric acid (GABA) system of the brain in the probiotic group. GABA receptor mRNA changes in the frontal cortex, amygdala and hippocampus via *Lactobacillus* broth administration were in line with expectations based on known effects of anti-depressant or anxiolytic chemical agents. Interestingly, the changes in behaviour and brain chemistry were largely extinguished with vagotomy (Bravo *et al.*, 2011).

Almost a decade ago it was argued that the local microbial production of GABA and other neurotransmitters may not be without consequence to emotional disorders (Logan and Katzman, 2005). For example, colonic bacteria are direct contributors to blood GABA levels (Schafer *et al.*, 1981). However, the clinical relevance of intestinal microbe GABA production was largely dismissed because it was generally held that circulating GABA does not penetrate the blood-brain-barrier. Recently, this has been called into question. Food rich in microbial-fermented GABA has been shown in experimental studies to have anti-depressant properties and influence brain neurotransmitter turnover in the hippocampus and amygdala (Chuang *et al.*, 2011). Moreover, preliminary clinical studies with a *Lactobacillus hilgardii* K-3 fermented GABA have shown clinical benefit in anxiety reduction and faster return to normalcy of stress physiology upon cognitive/emotional stress challenge (Abdou *et al.*, 2006; Nakamura *et al.*, 2009). On-going investigations are underway to determine the influence of orally administered fermented GABA products on the development of inflammatory skin conditions (Hokazono *et al.*, 2010). The extent to which this local GABA intestinal production can influence systemic physiology, depression and anxiety, is under investigation (Barrett *et al.*, 2012).

As the experimental gut-brain-microbiota research relates to the skin, it is noteworthy that the oral administration of *L. reuteri* to acoustically stressed animals did indeed lower inflammation within the perifollicular area of skin samples (vs. no probiotic controls) (Arck *et al.*, 2010). There are well-known similarities in signalling and innervations between the skin and the gut, and it is long established that cells of the brain, gut and skin are linked by common embryonic origin. Yet Arck *et al.* (2010) advanced the science by showing for the first time that oral probiotics can limit major histocompatibility cell (MHC) class II infiltration in the vicinity of hair follicles after the samples were removed from stressed animals. Dense accumulation of MHC class II cells were observed in the samples removed from the stressed animals. This landmark observation has

renewed international interest in the gut-brain-skin axis. Thus, taken together, is becoming increasingly clear that there are intricate and not yet fully understood pathways between gut microbiota, the nervous system and the skin.

The ability of probiotics to help attenuate substance P release in the skin and intestinal tract (Gueniché *et al.*, 2010b; Verdu *et al.*, 2006) is also of relevance in the pathway between the nervous system, gut, and skin. Experimental changes to the normal gut microbiota can increase nervous system release of substance P and promote anxiety-like behaviours (Collins *et al.*, 2009). Indeed, anxiety, depression and aggression can be induced by even minute elevations in circulating substance P (Herpfer *et al.*, 2007). Conversely, antidepressant pharmacotherapy is able to stimulate declines in serum substance P in responsive patients in conjunction with improved mood states (Lieb *et al.*, 2004). In experimental research, *L. paracasei* ST11 inhibits substance P-induced skin inflammation, while the oral administration of the same strain has been shown to improve skin barrier function and reduce local inflammation in animal models of skin inflammation (Philippe *et al.*, 2011). It has been thirty years since biologically active peptides such as substance P were discovered to not only communicate within the gut, brain and skin, but also derive from common embryonic origin (Teitelman *et al.*, 1981). With emerging research showing that substance P increases sebum production (Lee *et al.*, 2008), surely the gut-brain-skin pathway warrants serious investigation. An additional area of relevance between emerging probiotic research and acne involves the cannabinoid receptors. Experimental studies suggest that regulation of lipid production by sebocytes is under control of the cannabinoid receptor-2 (CB-2), a finding that takes on greater meaning given the preliminary findings concerning the ability of probiotic strains to influence CB-2 expression (Rousseaux *et al.*, 2007; Toth *et al.*, 2011).

The regulation of glycaemic control is an additional mechanism whereby probiotics might influence both mood and acne. In recent years, the dietary connection to acne has become evident; most notably, low-fibre carbohydrates have been associated with the risk of acne (Bowe *et al.*, 2010). For example, regional diets associated with decreased acne risk are low in processed foods and sugars, and feature an overall low glycaemic load. Indeed, intervention studies using similar low glycaemic load meals have reported improvements in acne (Rouhani *et al.*, 2009; Smith *et al.*, 2007). On the other hand, epidemiological studies show that there exists an elevated risk of depressive symptoms in healthy adults with blood chemistry indicative of insulin resistance (Pearson *et al.*, 2010; Timonen *et al.*, 2007). This finding is of relevance due to emerging research that shows that gut microbes may contribute to glucose tolerance (Kleerebezem and Vaughan, 2009). More so, the oral administration of *Bifidobacterium lactis* can improve

fasting insulin levels and glucose turnover rates, even in the presence of a high-fat diet (Burcelin, 2010).

Researchers are beginning to explore the mechanisms whereby probiotics might influence glycaemic control. For example, bifidobacteria appears to involve the species' ability to prevent the efflux of LPS endotoxins into systemic circulation. Specifically, the loss of bifidobacteria by poor dietary choices – high fat and sugar – leads to increased intestinal permeability and subsequent passage of LPS endotoxins through the intestinal barrier. The consequences of this include insulin resistance, low-grade inflammation, oxidative stress, and sickness behaviour (Cani and Delzenne, 2009). In humans, the administration of probiotics may diminish systemic access of gut-derived LPS endotoxins and also reduce reactivity to these endotoxins (Cani *et al.*, 2009; Schiffrin *et al.*, 2009). The whole picture discussed here acquires larger meaning when considering recent international studies that note the association of acne with increased intake of highly palatable, sweet, fried, calorie-rich foods with low nutrient density (Ghodsí *et al.*, 2009; Jung *et al.*, 2010; Wei *et al.*, 2010) and that humans undergo a well-known period of insulin resistance during puberty (Goran and Gower, 2001), coinciding with the development of acne, depression and/or anxiety. Therefore, it seems sensible to ask, to what degree might the gut microbiota influence these processes and the risk for acne, depression, and anxiety during puberty? A summary of potential pathways of interaction between the brain-gut-skin axis in acne is provided in Table 1.

We also find it significant that among three large population studies linking acne and dairy consumption (most notably skim milk), none found a positive correlation between fermented dairy (e.g. yogurt) and acne (Adebamowo *et al.*, 2006, 2008; Adebamowo *et al.*, 2005). Milk has been associated with acne because it contains both synthetically added and naturally occurring growth hormones (Melnik and Schmitz, 2009). Acne is clearly driven by insulin-like growth factor I (IGF-I) (Ben-Amitai and Laron, 2011), which can be absorbed across colonic tissue (Quadros *et al.*, 1994). Consequently, it is interesting to note that probiotic bacteria, specifically lactobacilli, utilise IGF-I during the

Table 1. Oral and topical probiotics – potential mechanisms of therapeutic value.

Reduction of local/systemic inflammation
Reduction of local/systemic oxidative stress burden
Inhibition of <i>Propionibacterium acnes</i> growth
Maintenance of intestinal barrier
Regulation of sebum production via cannabinoid receptor-2
Reduction of substance P-induced sebum excess
Influence on nutrient/omega-3 absorption
Stress resiliency via regulation of gut-to-brain communication

fermentation process when added to milk, and result in 4-fold lower levels of IGF-I in fermented vs. skim milk (Kang *et al.*, 2006). If our suspicions of increased intestinal permeability in acne are valid, the intestinal absorption of IGF-I would likely be enhanced, especially when skim milk, and not fermented dairy, is consumed orally. A 6-week study involving patients with type-2 diabetes showed that probiotic yogurt administration improved fasting blood glucose as well as systemic antioxidant enzyme activity and total antioxidant status (Ejtahed *et al.*, 2012). In sum, researchers need to look more closely at why fermented dairy has avoided an association with acne, while other forms of dairy have not.

8. Intervention studies

The first formal human study of the potential psychological benefits of probiotic supplementation involved 132 otherwise healthy adults. The results indicated that the otherwise healthy adults who were more depressed at baseline showed significant improvement in mood scores after consuming a probiotic *Lactobacillus casei*-fermented beverage vs. placebo group (Benton *et al.*, 2007). A different placebo-controlled study followed 39 chronic fatigue syndrome patients who were given the same oral *L. casei* probiotic in powder form vs. placebo. While depression scores remained unchanged between the groups at the conclusion of the 8-week study, there were significant improvements in anxiety vs. placebo as measured by the Beck Anxiety Inventory (Rao *et al.*, 2009).

French researchers recently employed a one-month placebo-controlled study to evaluate the oral administration of a *Lactobacillus helveticus* and *B. longum* combination probiotic. Utilising a variety of validated stress, anxiety, and depression scales, the researchers reported significant improvements in day-to-day anxiety, depression, anger, and also lower levels of the stress hormone cortisol among otherwise healthy adults taking the daily probiotic supplement vs. placebo. In addition, the study featured an experimental arm which confirmed that probiotic added to rat chow actually did decrease behaviours indicative of anxiety (Messaoudi *et al.*, 2011a). Moreover, given the research linking baseline depressive symptoms and improved mental outlook among healthy adults after probiotic administration, the French group performed a secondary analysis looking specifically at those with the lowest baseline urinary free cortisol (n=25). Indeed, the results once again showed improvement with *L. helveticus* and *B. longum* vs. controls (particularly in somatisation, depression and anger-hostility), and among the low cortisol sub-group the overall benefits in anxiety and depression were pronounced over time (Messaoudi *et al.*, 2011b). Another study showed that the oral consumption of a prebiotic fibre (trans-galactooligosaccharide) significantly reduced anxiety in 44 patients with irritable bowel

syndrome, in conjunction with the expected marked elevations in faecal bifidobacteria levels (Silk *et al.*, 2009). Finally, research has also provided evidence that the administration of the soil-based organism *Mycobacterium vaccae* can significantly improve depression, anxiety, and quality of life (vs. control) in lung cancer patients receiving chemotherapy (O'Brien *et al.*, 2004).

Certainly the publication of these studies must allow us to bear in mind the possibility that the psychological impairment seen in acne could, at least partially, be mediated by endogenous factors, surely including the gut microbiota. Over the years, a handful of researchers and clinicians have proposed the existence of an 'acne personality' that predates the onset of disease and subsequently increases the likelihood of anxiety, depression, and stress reactivity associated with acne (Blackburn, 1951; Lucas and Ojha, 1963; Narciso, 1952; Polenghi *et al.*, 2002; Wright *et al.*, 1970). Because most investigations have studied the post-acne psychological impairments, a commonly justifiable view is that the risk of depression and anxiety is strictly associated with the fact that the disease usually presents itself so visibly. It is not our position to infer that this view is incorrect; rather, we contend that some endogenous factors may also play a mediating role in the elevated risk of psychological conditions. We must ask why it is that even with remarkable clinical success with oral and topical interventions, a collection of studies using validated measurements of mood, depression, and quality of life indicates that the mental outlook remains unchanged (Kaymak *et al.*, 2009; Mulder *et al.*, 2001; Ng *et al.*, 2002; Winkler *et al.*, 2004)? Indeed, in one of the studies cited (Kaymak *et al.*, 2009), despite significant clinical improvement with topical treatments, mood scores still declined. Furthermore, a systematic review investigating depression and isotretinoin reported that only 1 out of 4 studies showed a statistically significant reduction in depressive symptoms using validated depression instruments (Marqueling and Zane, 2007). At least experimentally, the administration of retinoic acid has been associated with disturbances to the intestinal barrier (Oehlers *et al.*, 2012). It is remarkable that an agent with such obvious clinical benefit would merely show a trend toward improving depressive symptoms and mental outlook.

9. Future directions

It is now apparent that we can no longer neglect a potential relationship between the gut microbiota, mental health, and acne vulgaris. Just a decade ago, it seemed obscure to suggest that gut microbes may be a significant factor in the development of obesity. Yet, in the last several years an expanding body of research is highlighting a very significant relationship between gut microbiota, systemic low-grade inflammation, blood lipids, metabolism, and

fat storage (Musso *et al.*, 2010a; b). Incredibly, a recent study has shown that faecal microbiota transfer, using stool obtained from healthy lean donors, can beneficially influence insulin sensitivity when transplanted into the lower gut of individuals with metabolic syndrome (Vrieze *et al.*, 2012). Currently, there are many questions that require resolution. Are the regional differences in acne, for now simply linked to a low fibre, high glycaemic load diet, linked in any way to the relationship between such diets and the intestinal microflora? Isolated hunter-gatherer communities have been documented to have extremely low rates of acne (Cordain *et al.*, 2002); dietary and lifestyle habits in these groups almost certainly alter intestinal microflora directly via root fibre and also bring individuals into greater contact with a variety of beneficial soil-based organisms. Traditional lifestyles are associated with a more diverse gut microbiota profile (De Filippo *et al.*, 2010). On the contrary, we are aware that the typical Western diet is high in sugar and fat, deficient of fibre, and thus correlated with risk of acne; it is also associated with lower levels of gut *Lactobacillus* and *Bifidobacterium* (Benno *et al.*, 1986, 1989; Brinkworth *et al.*, 2009; Shinohara *et al.*, 2010).

The mechanism(s) of action of oral antibiotics in acne remains a mystery: is it an anti-inflammatory influence, a systemic effect against *P. acnes*, ability to lower sebum free fatty acids, and/or an antioxidant capability (Maffei and Veraldi, 2010; Toossi *et al.*, 2008)? Could it be due to the effects of antibiotics on the gut microbiota, which subsequently improves glycemic control and decreases LPS endotoxin invasion into the periphery (Membrez *et al.*, 2008)? Does there exist a substantial sub-population of acne patients wherein SIBO and intestinal permeability are playing a contributing role, connecting acne itself with a 'personality' predetermined to have a higher risk of depression and anxiety? In other words, might the gut microbiota-brain-skin relationship serve even a small role in the elevated rates of depression and anxiety in acne? We suspect that it does. As we discussed, the gut microbiota is able to influence systemic lipid and tissue fatty acid profiles. Therefore, it is practical to ask if the gut microbiota might influence overall sebum production as well as specific free fatty acids within sebum. It would be interesting to determine if oral rifaximin, an antibiotic that has no systemic antimicrobial activity, is effective in improving acne vulgaris, mood and quality of life, particularly due to its efficacy in SIBO-induced rosacea (Parodi *et al.*, 2008).

As we move forward, we must attempt to answer these and many other plausible questions. Acne vulgaris is a complex disease, with no single avenue of pathogenesis; therefore, scientists and clinicians must remain open-minded to unexpected and unique therapeutic pathways. Given the realities of loss of antibiotic efficacy and antibiotic resistance, exploration of novel pathways is an urgent matter. To date, Stokes, Pillsbury and other dermatology

elders have been validated in many regards, their work no longer sitting in history's dustbin. However, we cannot rely on inferences, anecdotes, and uncontrolled scientific observations. We must approach this exciting yet largely hypothetical landscape, the gut-brain-skin triangle, with scientific vigour.

10. Conclusion

For many years acne treatment has been plagued by dogma which has insinuated itself into dermatological teaching and textbooks (Bowe, 2010). Until recently, lifestyle habits, dietary practices and psychological stress have been relegated as being of little relevance in the pathophysiology of acne. It has also been broadly assumed that the psychological impairment noted in acne is strictly a product of the visibility of the condition itself. However, it has been suggested that dietary patterns and intestinal microbes may converge to influence nutritional status and the subsequent risk of psychological sequelae in acne (Katzman and Logan, 2007). Preliminary evidence described in this review supports this notion. Acne is emerging as much more than a skin disease; it is, rather, a multi-system disease.

Our understanding of the pathophysiology of acne continues to evolve, leading to new therapeutic targets and the development of advanced treatment regimens. The remarkable findings and insight related to nervous, immune and nutritional pathways as mediated by beneficial microbes have opened up multiple lines of potential investigation. Novel internal and topical interventions, ranging from probiotics/prebiotics to dietary factors which influence microbiota, are now worthy of vigorous research. There is much more to learn in the process of translational medicine, and for the patients who suffer from this ubiquitous and destructive disease, it won't be a moment too soon.

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