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The Microbiome and Mental Health: Looking Back, Moving Forward with Lessons from Allergic Diseases

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Relationships between gastrointestinal viscera and human emotions have been documented by virtually all medical traditions known to date. The focus on this relationship has waxed and waned through the centuries, with noted surges in interest driven by cultural forces. Here we explore some of this history and the emerging trends in experimental and clinical research. In particular, we pay specific attention to how the hygiene hypothesis and emerging research on traditional dietary patterns has helped re-ignite interest in the use of microbes to support mental health. At present, the application of microbes and their structural parts as a means to positively influence mental health is an area filled with promise. However, there are many limitations within this new paradigm shift in neuropsychiatry. Impediments that could block translation of encouraging experimental studies include environmental forces that work toward dysbiosis, perhaps none more important than westernized dietary patterns. On the other hand, it is likely that specific dietary choices may amplify the value of future microbial-based therapeutics. Pre-clinical and clinical research involving microbiota and allergic disorders has predated recent work in psychiatry, an early start that provides valuable lessons. The microbiome is intimately connected to diet, nutrition, and other lifestyle variables; microbial-based psychopharmacology will need to consider this contextual application, otherwise the ceiling of clinical expectations will likely need to be lowered.

KEY WORDS: Depression; Anxiety; Diet; Human microbiome; Microbiota; Allergy and Immunology.

INTRODUCTION

There is little doubt that the prevention and treatment of conditions associated with mental health is a critical issue of our time.[1,2] Mental, neurological, and substance abuse disorders now represent a substantial proportion of the world's disease burden.[3,4] In particular, major depressive disorder (MDD) and anxiety disorders are debilitating illnesses that are on a trajectory toward leadership within global burden of disease rankings.[3]

Mental health is described by the World Health Organization (WHO) not by the absence of disorder *per se*, but the ability of an individual to reach their potential, cope with normal stressors, work productively, and make contributions to the community.[5] Both MDD and subthreshold/subsyndromal conditions that do not meet full diagnostic criteria are important considerations in the risk of other non-communicable diseases (NCDs) such as Type II diabetes, cardiovascular disease, obesity and dementia.[6-10] Further, the WHO rightfully maintains that without mental health, there can be no true physical health.[11] However, the opposite is also true; chronic 'physical' NCDs can compromise mental health.[12,13]

There is little evidence to suggest that, in comparison to previous generations, recent cohorts in westernized nations are better off psychologically. Recent studies suggest just the opposite.[14-16] Pharmacological innovation in treatments for mental illness has lagged in the last several decades, and it is widely recognized that alternate approaches beyond the monoamine hypothesis—deficits in noradrenergic and serotonergic systems—are necessary.[17]

Despite their many differences, NCDs are most often

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united by the common threads of immune dysfunction and chronic, low-grade inflammation.[18-20] Depression, for example, is commonly associated with elevations in C-reactive protein, inflammatory cytokines and oxidative stress. Inflammation-induced consequences in the central nervous system can include altered neurotransmission.[21-24] As we will describe later, this may explain, in part, the high levels of overlap between NCDs such as allergic diseases and mental disorders.

The complex interplay between dietary patterns, psychological stress, environmental exposures such as pollutants, and lifestyle variables such as circadian disruptions and sedentary behavior, are of clear relevance to most, if not all NCDs. These factors can contribute to, or temper, the low-grade inflammation and biological dysregulations associated with depression and other NCDs.[25] This might be particularly true when the exposure/experience occurs in early life.[26,27]

It is also increasingly recognized that these environmental factors can impact upon human-associated microbiota (and their genetic contributions, including their non-living structural components; i.e. the microbiome).[28-31] The microbiome, in turn, may strongly influence overall health and the daily expression of our own genes.[32,33] Indeed, the recently observed relationships between anxiety and/or depressive symptoms and various dietary patterns, such as the westernized or traditional dietary patterns,[34,35] may be, at least partly, explained by the impact of diet and its components on the microbiome.[36] From an optimistic perspective, the determinants of immune system priming and resiliency against mental disorders may be modifiable by lifestyle changes, nutrition and psychopharmacetical interventions that target the microbiome.

The concept that diet can impact on human microbial ecosystems, which can in turn influence mental health, is the focus of the current review. This topic now gives rise to headline stories in popular magazines[37] and news pieces in leading journals.[38-40] However, amid the enthusiasm, it is helpful to review the history and identify pitfalls surrounding the growing focus on the microbiome and brain health. In particular, nearly two decades of research from the realm of allergy and asthma (combined here as allergy related diseases) has provided signposts for neuropsychiatry, and long-term intervention studies have already begun to highlight the shortcomings of viewing microbes as a stand-alone technological solution.

HISTORICAL ASPECTS

"*So early as Hippocrates, the abdominal viscera were regarded as the principal seats of disease in mania and melancholia. This doctrine has been, at various times, forgotten and revived from that period to the present moment, according as circumstances have occurred to influence the minds of the medical practitioners and as the opinions of the metaphysical or physical pathologists have prevailed.*"

David Uwins, MD,
Physician to the City of London Dispensary, 1818[41]

By the beginning of the 20th century, microbes were considered to be directly (and indirectly via their by-products released within the intestinal lumen) involved in various culturally-mediated diagnoses such as melancholic outlook, malaise, neurasthenia, and what were known as 'the neuroses'. Preliminary reports suggested that the administration of beneficial microbes could be helpful in cases of depression[42,43] and dietary alterations, especially macronutrients, were part of mainstream discussions concerning ways to manipulate intestinal microbiota for health.[44]

For example, manipulating dietary protein and carbohydrate in animals could induce changes in behavior with associated changes in the microbiota. The behavioral changes were attributed to a combination of both direct macronutrient influences on mood, and the indirect ability of foods to shift the production of mood-altering microbial byproducts.[45] Psychological stress was also part of the theoretical considerations as physicians speculated on potential pathways in chronic melancholia:

"*Disturbing the sympathetic and autonomic nervous centers as to result in disturbance of the digestive apparatus, such disturbance may lead to the development of an excess of certain bacteria...we need not even assume it is always the same bacterium which gives rise to symptoms like those of melancholia. Various antibodies and various metabolic by-products called out by the presence of bacterial enzymes, may be the particular poisons causing the 'cough' known as melancholia.*"

Robert T. Morris, MD, 1919[46]

As discussed in detail elsewhere,[47] some of the fledgling scientific findings during the 'bacterio-mania' of the early 20th century were groundbreaking. However, the science of so-called intestinal toxemia was rudimentary, and largely teetered on the theoretical; risky intestinal surgeries were performed to "rid" the body of its toxic reservoir, and the commercially lucrative 'microbial product' cart was placed before the proverbial horse.[47] This first

wave of serious interest in microbiota and mental health spanned from approximately 1900-1930, and left a legacy of unnecessary surgeries, useless products and unwarranted fears concerning frequency of what constituted normal bowel movements.

TOPIC IN EXILE

The end of the 'intestinal toxemia' era coincided with the dawn of the antibiotic era,[48] one that demonstrated clear, life-saving results based on simple intervention. Antibiotics shifted scientific thought back toward pathogens. Co-incident with antibiotic development, the cultural shift in mid-20th century westernized mental health care was also heavily weighted toward top-down (emotion to viscera) psychosomatics and scientifically unverifiable Freudian influences.[49,50] Then, with a growing focus on biological psychiatry, the monoamine theories of depression in the 1950-60s dominated drug development.[51]

During this period even noteworthy microbiological findings were approached with trepidation. In 1962, one of the most highly-respected microbiologists in mid-century America, Dubos and Schaedler[52] reported remarkable findings concerning the ways in which diet, antimicrobials and stress could influence growth, susceptibility to infections, and the lethality of systemic endotoxin —all in concert with changes to intestinal microbiota. However, they first had to contend with the historical legacy of intestinal toxemia:

"*The findings we wish to report here cannot help evoking memories of a quaint bygone scientific era. They call to mind Metchnikoff's assertions half a century ago that most of the ills of old age arise from intestinal intoxication, and that lactobacilli play a useful role in man and animals by antagonizing the noxious components of the intestinal flora. Today, Metchnikoff's imaginings are of interest only to a few historians, health cranks, and the manufacturers of yoghurt and acidophilus milk.*" [52]

Through the 1960s and early 1970s, Dubos and his colleagues published dozens of experimental studies implicating the intestinal microbiota in multiple aspects of health. Described elsewhere in detail,[53] his studies focused on microbiota, diet, and other environmental variables. For example, Lee and Dubos[54] reported that when female specific-pathogen-free mice are fed low quality protein during the perinatal period, the brain content of dopamine and norepinephrine in offspring is diminished. They concluded that "*Metchnikoff's concepts of intestinal intoxication may have some factual basis after all"* and that they were *"inclined to believe that the usual intestinal flora is an expression of man's total environment, and that its control may turn out to have as profound effects on the well-being of human infants and adults as it has on the growth of mice and farm animals*".[52]

Studies by Dubos and his colleagues went largely unreferenced and the concept of beneficial microbes for mental well-being was certainly a neglected subject through the remainder of the 20th century. The proposition that the intestinal microbes are collectively a distinct organ[55] was given little credence. Notions of a connection between the intestinal microbiota, the integrity of the intestinal lining, and the systemic influence of microbial toxins on mental/neurological health (save for advanced pathogenic conditions; e.g., hepatic encephalopathy) were considered to defy the prevailing logic.[47]

LESSONS FROM ALLERGIC DISORDERS, HYGIENE HYPOTHESIS

"*Psychoimmunologic research has often had a unidirectional focus from the mind to the immune system—e.g., immune dysfunction in individuals with and without psychosocial stress...the field should also consider the other direction for central nervous-immune system interactions, i.e., possible affective dysfunction in individuals from additive or synergistic immunological events.*"

Iris R. Bell, MD, *et al*. 1991[56]

As the 20th century drew to a close, one avenue of intestinal microbiota and health research did remain open: allergy related diseases. Much of this field was built upon the hygiene and microbial deprivation hypotheses. Jointly they proposed that the global rise in allergic disease could be related to diminished opportunity for early life exposure to pathogenic microbe exposure and overall microbial diversity via increased hygiene, antibiotics, smaller family sizes, altered dietary patterns and other environmental factors.[57-59]

Allergy and asthma research *circa* 2000 promoted a focus on the modern intersection between diet, external environment, and microbes.[59-64] Omega-3 fatty acids were posited to be important for prevention and treatment of allergy-related diseases.[65] Lactic acid bacteria and fermented foods were proposed to attenuate allergic disease via their influence on the immune system and T helper cell 1 and 2 (Th1/2) balance,[66-68] although there was no specific connection to mental or cognitive health.

However, the overlaps between allergic disorders, chronic fatigue/chronic fatigue syndrome (CFS), depression and anxiety were noted to be extraordinarily high.[56] Subsequently, in 2002, a new perspective on the intersection between allergic disorders (and other immune abnormalities) and mental health led to an entirely new proposal - that *beneficial* microbes may play a role in neuro-cognitive functioning and behavioral disturbances via immune and other pathways.[69]

Pioneering research around that time (using culture techniques) had already connected certain fecal microbial communities with neurological and cognitive deficits in fatigue and functional syndromes.[70] It had also been shown experimentally that orally administered *Campylobacter jejuni* (without overt immune activation) produces anxiogenic effects and activation of visceral sensory nuclei in the brainstem. This suggested that even in the absence of major immune shifts, autonomic, neuroendocrine and behavioral responses to miniscule amounts of gut bacteria were possible.[71] The vagus nerve was at least one pathway (but not the only route) whereby information concerning microbiota could be transmitted from the gut to the brain.[72]

In 2001, a landmark study showed that very low levels of endotoxin in the blood can provoke cytokine release, alter cognition, and diminish mental outlook in humans.[73] And so it became theoretically realistic that there would be mental health consequences if the intestinal barrier was compromised. In popular writing, the description for this state of increased intestinal permeability (IP) was 'leaky gut'.[74] Since the largest reservoir of microbial endotoxin (lipopolysaccharide [LPS] endoxin in particular) is within the intestinal tract, this research opened the door to the mood-related consequences of IP.

Currently IP is under increased scrutiny as a key contributor in the causal pathways to chronic conditions such as asthma,[75] allergies,[76] depression and CFS.[77,78] IP is also associated with alcohol use disorder,[79] obesity,[80,81] fibromyalgia,[82] extremes of exercise,[83] and psychological stress.[84] Experimentally, an increased LPS burden can increase toll-like receptor activation in the brain, which in turn can increase central nervous system inflammatory mediators and oxidative stress.[85] The dietary influences on IP are discussed in more detail below.

Adding to the interest in beneficial microbes for mental health, novel probiotic studies began to emerge in the early 2000s. Using experimental models, researchers showed that probiotics can benefit intestinal barrier function.[86] Other groups showed that oral probiotics can influence systemic markers of immune activation and oxidative stress in humans.[87,88] These studies provided further theoretical possibilities that beneficial microbes could be systemic mediators of neurological effect. Additional potential mechanisms include direct and indirect effects on neurotransmitter/neuropeptide production, enhancement of nutritional status, and more direct bacteria-to-brain communication (Fig. 1).[69,89]

An influential 2004 study reported that gene expression of a primary nerve growth factor, brain derived neurotrophic factor (BDNF), was lower in the hippocampus and the cortex of germ-free (GF) animals compared with conventionally-raised specific pathogen-free animals.[90] As BDNF plays a critical role in the plasticity of nerves throughout life, this indicates that commensal microbes are capable of influencing brain structure and function. The study also showed that GF mice had enhanced hypothalamic-pituitary-adrenal axis activity following acute stress, demonstrating that microbiota are involved in programming the stress response. An overlooked, but no less important study also showed that conventionally-raised animals (vs. GF) have higher levels of histamine in the hypothalamus.[91] Today, the importance of histamine, BDNF and other nerve growth factors are central in discussions of brain health.[92,93]

- Direct protection of the intestinal barrier
- Influence on local and systemic antioxidant status, reduction in lipid peroxidation
- Improvement of nutritional status-e.g. omega-3 fatty acids, minerals, dietary phytochemicals
- Direct, microbial-produced neurochemical production (e.g., GABA)
- Indirect influence on neurotransmitter/neuropeptide production
- Prevention of stress-induced alterations to overall intestinal microbiota
- Direct activation of neural pathways between gut and brain
- Limitation of inflammatory cytokine production
- Modulation of neurotrophic chemicals including brain-derived neurotrophic factor
- Limitation of carbohydrate malabsorption
- Limitation of small intestinal bacterial overgrowth
- Reduction of amine/uremic toxin burden
- Limitation of gastric/intestinal pathogens (e.g., *Helicobacter pylori*)
- Analgesic properties

Fig. 1. Beneficial microbes for fatigue and depression; originally proposed pathway. Adapted from references 57, 78, and 225.

ADVANCES IN RESEARCH

In recent years it has become even more clear that there are bi-directional relationships between depression and/or anxiety disorders and the subsequent risk of asthma, and *vice versa*.[94,95] Indeed, maternal depression and anxiety in pregnancy may increase the risk of allergic disorders in offspring.[96] Despite the heterogeneity of CFS physiology, evidence now indicates that a shift to a Th2 immune response (and away from Th1) is most characteristic of the syndrome. Interestingly, allergies in general, and allergic rhinitis in particular, have been noted to predate the subsequent onset of CFS.[97] The multi-system complexity of CFS has made this a proving ground for understanding the relevancy of the immune system to mental health, allergies, so-called functional gastrointestinal disorders (e.g., irritable bowel syndrome) and microbiota.

Sequencing technologies and inventories of the 16S rRNA gene have overcome some of the drawbacks of culture-only techniques, and allowed for detailed characterization of microbial ecosystems in intestinal, oral and cutaneous samples. There is mounting evidence that patients with depression[98,99] or CFS[100,101] show distinctions in their intestinal microbiota. Moreover, emerging research continues to show that diminished microbial diversity in early life can place an individual on a trajectory toward increased risk of allergic diseases.[102,103] Specific changes in fecal microbiota may not necessarily be the same throughout NCDs, however the new findings help to further clarify the ways in which the common NCD threads of immune dysregulation and chronic low-grade inflammation could impact upon, and be affected by, microbial factors.

As for research in dietary patterns, the evidence continues to grow in both the realms of allergic disorders and mental health. From a temporal perspective, the study of nutritional factors in mental health, especially dietary patterns, is a more recent phenomenon that has risen in concert with the gut-brain-microbiota research. A decade ago, diet and nutrition were not mainstream in neuropsychiatry conversations. Even in allergy, the focus of nutrition was minimal prior to the global rise in frequency of food allergy.[104] This has now shifted the spotlight to early gastrointestinal events in the breakdown of oral tolerance—a factor that may be equally relevant to the rising rates of neurodevelopmental disorders. Today, there seems little doubt that overall diet and specific nutrients are of critical importance in optimal development and mental health.[23]

While many questions remain, the general themes in mental ill-health, allergy and other inflammatory disorders are quite similar, including their environmental risk factors. Dietary patterns that more closely resemble traditional, less-processed diets (e.g., Mediterranean model) appear protective against the risk of allergies, asthma, depression and other NCDs that have been associated with dysbiosis and immune dysregulation. On the other hand, higher consumption of fast foods and highly-processed foods—those that more closely resemble what is now known as the 'westernized' dietary pattern—have been associated with a higher risk of the aforementioned conditions.[19,20,105,106] These conditions also share early life risk factors, many of which determine life-long propensity to inflammation.[107] These are increasingly viewed from a 'developmental origins' perspective, particularly as epigenetic mechanisms are becoming better understood (as discussed below). Therefore, early disruptions in microbial diversity and their linkage to allergic outcomes and neurobehavioral disorders[102,103,108] adds to our understanding of the early life origins of immune dysregulation as an antecedent event in many NCDs.

MICROBIOTA: RODENT STUDIES

The emerging potential of microbial manipulation for mental health rests upon groundbreaking studies involving rodents. Notwithstanding the multiple limitations concerning the application of rodent studies to the human condition in general,[109] and human microbiota and complex mental health in particular,[110-112] these studies have certainly proved insightful and established a much-needed foundation that includes potential mechanisms.

The vagus nerve is a confirmed conduit for promoting anxious behavior following induction of intestinal inflammation, and of anxiolysis following administration of a probiotic.[113] Probiotic supplementation to healthy animals reduces anxiety and depression-like behavior in various models of stress-induction.[114] Critically, behavioral changes are associated with changes in the expression of gamma-aminobutyric acid (GABA) receptors in areas of the brain governing emotion. Again, the vagus nerve appears to be the channel between beneficial microbes, behavior and brain chemistry.[114] Beneficial microbes are also known to suppress histamine signaling in allergy models.[115]

Another classic experimental model involves fecal microbial transfer. In GF BALB/c mice, a strain with known deficits in sociality and diligent risk assessment of the environment,[116,117] colonization with microbiota derived from more 'explorative' NIH Swiss mice changes the be-

havior of the BALB/c recipients—with more explorative behavior in the weeks following. On the other hand, when NIH Swiss mice are colonized with the BALB/c microbiota, they display greater hesitancy.[118] Such behaviors are indicative of both anxiety and *in situ* risk taking. Animal research also shows that probiotic pretreatment prevents decreases in hippocampal neurogenesis typically induced by stress, and favorably influences the expression of hypothalamic genes involved in synaptic plasticity. Interestingly, these effects in the brain are linked to the ability of the probiotic to mitigate stress-related IP.[119]

Upregulation of oxytocin provides another novel pathway for the systemic action of probiotics and the microbiota in general.[120] This neuropeptide hormone is connected to pair bonding, regulation of circadian rhythms,[121,122] prevention of IP[123] and is emerging as a significant target of drug development for the treatment of psychiatric disorders.[124] Interestingly, since oxytocin can also modulate risk taking and the saliency of social cues,[125] this might explain probiotic/fecal transfer-induced risk taking in otherwise risk-averse, anxious mice.

Further highlighting the links between inflammation, metabolic disease and the brain, faecal transplants in murine models of obesity also illustrate the microbiota-dietary connection. When lean, healthy mice (consuming standard laboratory chow) are the recipients of fecal microbiota derived from donor mice raised on a high-fat diet, significant behavioral changes are observed. These include signs of anxious behavior, cognitive difficulties and stereotypical, repetitious behavior.[126] Moreover, the production of short-chain fatty acids (e.g., butyric acid) by microbial activity on dietary fiber may play a key role in the development and function of microglia.[127] Short chain fatty acids derived from the colon may be able to pass the blood-brain barrier and influence transcellular neurotransmitter cycles.[128] Since normal-functioning microglia are essential in striking the optimal balance between host defense and synaptic plasticity (over-activation has been linked to neuroinflammation), the ways in which environmental factors influence both gut microbiota and neurochemistry are probably not yet fully realized.

BENEFICIAL MICROBES: HUMAN RESEARCH

There have been a number of human intervention studies involving beneficial microbes and mood-related outcomes.[129-137] To the best of our knowledge, there has yet to be an intervention study involving microbes and patients with MDD or anxiety disorders. However, the benefits observed in the available clinical studies suggest that a movement toward trials involving patients with depression, anxiety, or subsyndromal disorders is warranted. Highlights of human research are presented in Table 1. In our opinion, this provides room for optimism concerning the potential value of beneficial microbes.

These studies are bolstered by the experimental studies

Table 1. Select human studies involving probiotics

Subjects/Condition	Beneficial microbe(s)	Duration	Beneficial outcome
(131) Healthy adults (n=124)	*Lactobacillus casei* Shirota	3 Weeks	Those in the bottom 1/3 of the group initial scores on POMS reported feeling happier and less depressed
(130) Laryngeal cancer (n=20)	*Clostridium butyricum* Unspecified strain	2 Weeks, pre-surgery	Lowered serum corticotropin-releasing factor, heart rate; reduced HAS scores pre-surgery
(132) Chronic fatigue (n=39)	*L. casei* Shirota	8 Weeks	Improved scores on BAI vs. baseline
(135) Healthy adults (n=44)	*L. gasseri* OLL2809 heat inactivated	4 Weeks	Decreased tension-anxiety on the POMS
(137) Healthy adults (n=40)	*Bifidobacterium bifidum* W23 *B. lactis* W52 *L. acidophilus* W37 *L. brevis* W63 *L. casei* W56 *L. salivarius* W24 *L. lactis* W19/W58	4 Weeks	Reduced self-reported cognitive reactivity to sad mood; reduced aggressive/ruminative thoughts. Measured via Leiden Index of Depression Sensitivity
(133) Healthy adults (n=55)	*L. helveticus* R0052 *B. longum* R0175	4 Weeks	Lower global severity index on the Hopkins Symptom Checklist 90; Improved depression anger-hostility and somatization; lower anxiety on the HADS
(136) Infants with atopy risk (n=75)	*L. rhamnosus* GG	24 Weeks post-birth	Physician-diagnosed attention-deficit hyperactivity or Asperger syndrome (ICD-10 criteria at age 13 years) is lower

POMS, the Profile of Mood States; HAS, Hamilton Anxiety Scale; BAI, Beck Anxiety Inventory; HADS, Hospital Anxiety and Depression Scale; ICD-10, International Classification of Diseases 10th revision.

described earlier, and by other human studies that indicate value of microbes and microbial-transformed foods in objective markers of stress physiology,[138] brain activation,[139] and 'quality of life' improvements in other medical conditions.[140-142] On the other hand, the extremely limited nature of the current body of human research should be recognized. In addition to the absence of specific mental health disorders, the small sample size of the published studies mean that the field can only be described as preliminary.

ODYSSEY TO TRANSLATION–DIET AS THE COMPASS

Although the last word is far from written, it is clear that dietary patterns and specific combinations of nutrients such as omega-3 fatty acids, zinc, magnesium and plant phytochemicals are of relevance to depression and other mental disorders.[143] Epidemiological studies have reported that more traditional dietary patterns are associated with good mental health and lowered risk of depression.[144-148] Short-term intervention studies show that traditional dietary patterns can positively influence mental outlook, cognition and chronic fatigue.[149-151]

As the idea of targeting the microbiome for mental health begins its long trek toward translation, it would seem obvious that diet may be the "rate limiting step" in the chain reaction that otherwise might allow microbes to work toward long-term mental health. At virtually all junctures of the known and theoretical mechanistic pathways by which microbes could influence brain health (Fig. 1), diet is an undeniable focal point. Perhaps the easiest way to illustrate this is to examine the consequences of maintaining a westernized dietary pattern.

The modern westernized diet is distinct from traditional, ancestral dietary patterns in two fundamental ways. Firstly, by its much higher content of ultra-processed foods, added fats, sugar and sodium. Secondly, by what it excludes—relatively unprocessed plant foods, fermented foods, phytochemical-rich foods, fiber, and fats that are embedded naturally within foods (e.g., unprocessed meats, fish). The available evidence from communities who still maintain traditional (relatively non-western) lifestyles demonstrates that, among other environmental variables, the avoidance of a westernized diet and inclusion of traditional foods is a pathway to diversity and species richness of intestinal microbiota.[152-157] While researchers do not have a complete understanding of what constitutes a healthy intestinal microbiome, a generalized finding is that diversity may prevent metabolic dysregulation and favor health promotion.[158,159]

Moreover, once a westernized dietary pattern is in place, it can be associated with sub-optimal intake (if not overt deficiencies) of essential fatty acids, vitamins and minerals.[160] Given the high fructose and sodium,[161] the dietary advanced glycation endproducts, and food additives that are consumed via processed foods,[162,163] together with inadequate omega-3,[164] excess alcohol consumption[165] and low levels of vitamin D[166,167]—each individually associated with marked shifts in the intestinal microbiota—the implications of dietary patterns in relation to the microbiome are clear.

Since the western diet is relatively devoid of deeply-colored fruits, vegetables and other plant-derived culinary items (e.g., turmeric, ginger, seaweeds, purslane, wasabi, Brassica-family sprouts, and regional spices) this represents a loss of complex phytochemicals that would otherwise make their way into the gastrointestinal tract. These phytochemicals play crucial roles in support of the antioxidant defense system, and in their ability to reduce the low-grade inflammation. In experimental studies, dietary phytochemicals from turmeric, apples, grapes, plums, blueberries and cherries (to cite only a few examples) can improve behavioral aspects of stress, anxiety and depression.[168-171]

It is interesting to note that dietary items such as green tea, coffee, cocoa, curcumin, and other polyhenol-rich foods associated with fatigue reduction, positive mood and lowered risk of depression in humans[172-175] can also influence the growth of beneficial bacteria, and/or prevent dysbiosis in pre-clinical settings.[176-179] The transformation and structural alteration of many dietary phytochemicals by intestinal microbes may determine the extent of their benefits in the brain.[180] Remarkably, it also appears that microbially-transformed phytochemicals (e.g., quercetin after it has been subjected to fermentation) can modify the gut microbiota in ways that are considered healthy (i.e., growth of bifidobacteria and decrease in the ratio of Firmicutes to Bacteroidetes).[181]

The Westernized dietary pattern also appears to play a central role in provoking IP and its systemic inflammation-based consequences.[182] However, phytochemical-rich foods and beverages may be able to prevent the typical elevations in circulating endotoxin when co-consumed with western dietary choices.[183] In experimental models, various phytochemicals have been shown to protect the intestinal barrier and prevent IP; these include but are not limited to curcumin, green tea catechins, quercetin

and resveratrol.[184-186]

In addition, omega-3 fatty acids may play a particularly important role in preventing IP. Specifically, it is an increase in tissue omega-3 levels that appears to lead to a beneficial cascade of events—via higher intestinal alkaline phosphatase—that include modification of gut microbiota, lower LPS production, and decreased IP.[187] This is notable because tissue omega-3 levels may be low in depression, and omega-3-based interventions have been shown to have clinically-meaningful value in treatment and prevention of mood and anxiety disorders.[188] There is also preliminary evidence suggesting that omega-3 fatty acids may reduce the risk of infant sensitization to foods such as egg.[189] Indeed, the westernization of dietary patterns typically includes marked increases in omega-6 rich vegetable oils; this may translate into lower relative tissue concentrations of omega-3 fats.[190]

SIMPLE FOOD, SINGLE NUTRIENT HIGHLIGHTS COMPLEXITY

Further identification of the importance of dietary constituents *vis a vis* microbiota and mental health can be found in the experimental research on honey. It is high in phytochemicals, particularly those in the phenolic acid and flavonoid families.[191] Several pre-clinical studies indicate that honey has antidepressant and anxiolytic properties.[192,193] Remarkably, honey flavonoids have been shown to show significantly inhibit the release of pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin-1 beta from microglia when they are stimulated by LPS.[194] It is no less noteworthy that honey and its constituents appear to have a beneficial influence on intestinal microbiota.[195,196]

Dietary magnesium (found within deeply colored green vegetables) represents another simplified example of the way in which nutrition cannot be isolated from microbe-mental health conversations. Several studies have shown that low magnesium (and/or low dietary intake) is associated with depressive symptoms and anxiety.[197] In experimental studies, low dietary magnesium intake alters the microbiota, which in turn is linked to inflammatory cytokine release in the brain and signs of anxiety and depressive behavior.[198,199] Much like honey, magnesium also inhibits the inflammatory consequences of LPS-stimulated microglia.[200]

EPIGENETICS AND THE FIRST 1,000 DAYS

Epigenetics includes the study of the ways in which alterations in chromatin structure can influence gene expression via mechanisms that do not involve changes to the primary DNA sequence. Two of the best-studied epigenetic signals include DNA methylation and histone modification. Despite the complexity of epigenetics, it is becoming increasingly clear that epigenetic regulation can play crucial roles in the fate of the functioning of the immune system, and that bio-environmental factors—including diet and microbial-generated products that are determined by dietary choices (such as butryrate)—are central to epigenetic modifications that could orient immune programming toward health.[201]

There is much hope in early interventions that could be directed toward allergic disease and mental disorders. Aforementioned dietary phytochemicals such as quercetin, curcumin and catechins are known epigenetic modifiers.[202] It is likely that the greatest impact of microbe-based psychopharmacology (see "psychobiotics" below), including those that could influence epigenetic signals, will be evident in early life. Extensive international research supports the developmental origins of health and disease (DOHaD) construct, which suggests that early life environmental experiences, particularly those encountered in the first two years of life, predict subsequent NCD risk.[203]

The quality of perinatal nutrition has been associated with subsequent mental health outcomes.[204] Moreover, long-term follow-up of a project which was originally initiated to examine early-life probiotic intervention to prevent allergy, has indicated there may be value in the prevention of brain-related conditions (attention-deficit hyperactivity and Asperger syndrome) at 13 years of age.[135] Epigenetic mechanisms are an important part of the DOHaD discussions, especially as they relate to allergic and mental disorders.[205,206]

It is possible that targeting the gut microbiome early in life with microbial-based products could help to overcome the environmental forces that might otherwise set up epigenetic signals that direct toward increased NCD risk. One such environmental factor includes maternal and early-life antibiotic use.[207] Although early-life antimicrobial use has been the subject of much research in allergic disease (and more recently, obesity),[208] less is known concerning subsequent mental health. It is difficult to paint all antimicrobials with the same brush; however, some experimental studies suggest that they can induce behavioral changes, including anxiety.[209-211]

PSYCHOBIOTICS IN CONTEXT

'Psychobiotics' is a recently-coined term referring to beneficial microbes that may provide value in cases of diagnosed mental disorders. Introduced in 2013, the term refers to "*a live microorganism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness*".[212] This definition is a good fit for commercially-driven product development wherein the microbes must be living and are intended for use specifically in cases of psychiatric illness.

The term psychobiotic, as currently defined, may be too narrow. Non-living microbes are excluded, as are microbial parts such as DNA. Yet, human subject research shows value of heat-inactivated microbes in mental health and allergic disorders; this may be via their influence on the immune system and markers of stress physiology[134,213-216] Moreover, the microbial components, even at the genetic level, have been shown to influence physiology.[217,218] Narrow views toward single (or a few) microbe solutions may neglect the microbial contexts and synergies that produced such startling preliminary research in the first place. One concern is that a focus on narrowly defined psychobiotics might cloud broad discussions of microbial ecosystems. Looking to the realm of post-hygiene hypothesis allergy research, it becomes plain to see that interventions with single (or select few) microbes have not always produced the desired outcomes over the long-term.[219-222]

We can also look to emerging research concerning the microbiome and obesity as a way to highlight the inherent perils of microbial solutions viewed apart from environmental realities. In GF animal studies involving transfer of fecal material derived from lean and obese mice and/or human twins, there seems little doubt that an obesogenic microbiome can influence metabolism and energy storage. However, the ability to overcome this is diet-dependent.[223,224] In other words, it may be difficult to realize long-term metabolic and immune benefits after obtaining a fecal transplant from a healthy donor, if default westernized dietary practices remain in place.[31]

On the other hand, as mentioned above, many of food/herbal-derived phytochemicals associated with mental health are also known to prevent dysbiosis. Research on microbes found in fermented foods and/or the action of microbes upon phytochemicals demonstrates that microbes could potentially influence mental health by virtue of their ability to transform the food. Transformation during fermentation could lead to novel therapeutics via newly-formed and/or more bioavailable phytochemical structures and peptides.[225]

In a recent study involving over 700 young adults, it was reported that fermented food consumption was associated with less social anxiety, and specifically, among those with high in neuroticism scores, greater frequency of fermented food consumption was associated with fewer symptoms of social anxiety.[226] Fermented food consumption is also associated with a lowered risk of developing allergic disorders in children.[227] In addition, the structural parts of heat-inactivated microbes (those associated with fermented foods) are also consumed, and these may also have far-reaching effects on intestinal ecosystems.[228] Beneficial microbes carried on/within fruits and vegetables might also influence the human immune system.[229] Remarkably, very little is known concerning the microbes, both viable and non-viable, that are directly consumed as part of daily meals.[230]

CONCLUSIONS

The microbial-mental health realm has a somewhat checkered past. At the beginning of the 20th century, major advances were making intestinal microbes part of mainstream discussions. In their own era, urinary indican and the identification of intestinal by-products (such as putrefactive amines), and the early reports of beneficial microbes (oral and commensal fecal transfer) for mental health were revolutionary.[47]

Awareness of this history is, in our opinion, quite important. There are many parallels to be found in some of the unbridled enthusiasm with which microbial biotechnological solutions are proposed today. We must also begin to query the limitations and environmental contexts in which microbes are to be applied. Stress can induce systemic inflammation, and differing dietary patterns (low-fat vs. high-fat and westernized) can influence weight and body-fat storage, by mechanisms independent of intestinal microbiota.[231,232] Therefore, we must not be tempted to view complex NCDs as if they were *Clostridium difficile* infections where problem and microbial solution are more neatly defined.

Human mental health and allergic disorders, and other NCDs rooted in chronic low-grade inflammation, even in their early origins, are as complex as the microbial ecosystems from which these isolated microbes are removed. Thus, single-strain prevention strategies have many obstacles to overcome. From the treatment perspective, the odds of long-term, clinically-significant benefits of mi-

crobe-based products would also seem slim if the environmental factors driving toward dysbiosis remain in place.

There are, however, reasons to suspect that supplementation with beneficial microbes can provide synergistic support to established mental health interventions. There is a generally good safety record of probiotics, even in children.[233] Given the gastrointestinal side-effects of prescription psychotropic medications, and the unknowns concerning their effect on human microbiomes,[234] supplementation with beneficial microbes, may provide important value.

The available evidence from allergic diseases concerning nutritional influences on epigenetic programming[235] clearly indicates that a whole food dietary composition approach (vs. isolated nutrients) is far more likely to augment the clinical value of microbial psychopharmacology. With already well-documented collateral health benefits,[236] and emerging research demonstrating specific mental health value,[226] fermented foods represent a gateway to the discussion of healthy dietary patterns and the intestinal ecosystem. One of the most exciting, if not daunting, aspects of the microbiome revolution is that it forces an even more assiduous clinical consideration of the importance of healthy lifestyles.

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