

The Oral Microbiome: Health Benefits, Disease, and Neurodegeneration

Keywords

Adaptive immunity; Bacteria; Diet; Microbiota; Microbiome; Oral cavity; Neurodegenerative disease

Abstract

It is a well-known idea that humans have a large set of bacteria housed inside them, but it was not until the year 2001 that Joshua Lederberg would officially coin the term 'microbiome' in reference to the ecological community of commensal, symbiotic and pathogenic microorganisms that share our body space. Since that time, the advancement of technology has allowed for much more efficient sequencing and studying of the exact microbiota dwelling symbiotically within humans. The oral cavity houses the second highest amount of microbiota in the human body, 700 species, only behind the gut which boasts over 1,000 different bacterial species. This review article explores the large database of research that supports the complex relationship humans have with the bacteria inside them. Many different factors contribute to the formation of a person's oral microbiome including a person's lifestyle and diet choices, as well as societal factors such as antimicrobial and pesticide use. Research has suggested that the relationship between microbiome and host is constantly changing to meet the ever-changing conditions pertaining to human life. While some bacterial species can be assistive in helping humans develop adaptive immunity and biofilms, other species can contribute to health complications such as gingivitis, dental caries, and even neurodegenerative diseases. While a lot of research is still needed to establish exact mechanisms on how these bacteria acquire entry into other parts of the body and the central nervous system, it is clear that their impact expands farther than just their oral cavity home. Bacteria in conjunction with human life cannot be seen as all-assistive or all-destroying. Depending on the bacteria present and its location within the body, its effects can be extremely life-sustaining or extremely life-threatening.

Introduction

From a very young age kids are taught that germs are bad. They are strongly advised to wash their hands for the entire duration of the ABCs in order to cleanse themselves from any remaining bacteria they had acquired while playing outside in the mud. The fact of the matter is that though we may try to rid ourselves of microorganisms, they are impossible to escape. It is estimated that the human body houses around 30-50 trillion bacterial cells at any given point [1], a number that is sure to make any parents of a toddler squirm. In actuality, while some bacteria are harmful and can foster the spread of pathogens and neurodegenerative diseases, a large proportion of bacteria dwell symbiotically within us, helping us perform various bodily functions that would otherwise not be possible. Most review articles tend to focus on a single topic concerning the oral microbiome, be that the benefits, the oral diseases or the neurodegenerative implications these bacteria have on humans. However, there is an extremely large overlap in the role that bacteria can play. For instance, Tomás et al. in 2012 discuss one type of bacteria that leads to plaque formation, yet also hinders the growth of some more dangerous bacteria in the same area [2]. For this reason, it is extremely difficult to separate the good, the bad, and the ugly that this microbiota elicit in the human body.



Journal of Oral Biology

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Submission: 22 June, 2019

Accepted: 03 August, 2019

Published: 06 August, 2019

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It is the goal of this review article to give the reader a more holistic understanding of all the roles that these bacteria can play, as well as to give insight on how our own lives and the lives of said organisms have become even more connected in terms of immune system and overall health than was previously believed. With this paper, we seek to answer the question: what purpose do these microorganisms serve and are they primarily good or bad? These bacterial populations are dynamic in nature, adapting daily to new environmental factors and lifestyle choices that humans make without even thinking about it.

Factors Affecting the Oral Microbiome

The first factor that greatly impacts the oral microbiome is the dietary choices of humans. Studies have looked at the progression of bacteria. Over the course of human history there have been two major shifts in microbiome occupancy [3]. The first shift came during the transition from a hunter-gatherer lifestyle to an agriculturally based lifestyle about 10,000 years ago [4]. There is evidence that during prehistoric times when our ancestors were primarily hunters and gatherers, there were a lower number of cariogenic bacteria or bacteria that can cause tooth decay [5]. Despite this, the oral microbiome was still very diverse accommodating the vast variety of foods that these hunter-gatherers would eat.

During the onset of the farming lifestyle when consumption of carbohydrates such as wheat and barley greatly increased, there was a positively associated increase of these cariogenic bacteria as well [6]. It was at this time that tooth decay and periodontal disease started to present themselves. These two diseases are both brought about by the buildup of plaque. Plaque development occurs when a bacterial biofilm mineralizes with calcium phosphate. After mineralizing the plaque is deposited around the gingiva or the gums [7]. The second shift of diet was during the industrial revolution between the years 1760 and 1830. This can most likely be attributed to the newly developed means of food production including machinery as well as new preservatives to extend the shelf life of foods [8]. It was at this point that the once absent cariogenic bacteria actually became the dominant species resulting in a large decrease in bacterial biodiversity

in the oral cavity. Research suggests that this shift in diversity and prevalence of cariogenic bacteria is one of the primary causes of 92% of adults having tooth decay in their lives and half of American adults having chronic periodontal disease [9].

Linked with diet, poor oral hygiene has a profound influence on the oral microbiome. Common observances noted among patients with poor oral hygiene include, a high plaque index, generalized cervical calculus, rampant caries, halitosis, and low salivary flow [10]. These clinical findings are closely tied to long-term acidification. Without proper care and clinical treatment, these factors cause the pH of the oral environment to fall below a pH of 5.0. This decrease in pH causes particular bacteria to dominate the oral microbiome. More specifically, members of the genus *Streptococcus*, *Capnocytophaga*, *Eikenella*, *Campylobacter*, and *Actinomyces* all increase inviability in the mouth without proper oral care. These forms of bacteria are mainly from the yellow, green, and purple complex of subgingival microbiomes. These groups are early colonizers of the tooth surface, and their growth typically precedes the predomination of gram-negative orange and red complexes [11].

The next factor that impacts the oral microbiome is antimicrobial use. With the exponential growth of the human population we have needed to just as quickly adapt our food production styles. One way we have chosen to make this adaption is through the use of antimicrobials and pesticides. From this increased exposure to avoparcin and other antibiotics, some bacteria have developed partial or complete immunities to certain drugs such as vancomycin or chemicals in human saliva [12]. Because of this immunity, some types of bacteria housed in the oral microbiome have flourished, increasing in number. Depending on the bacteria, this can be either a good or bad thing. One example is the bacteria *Staphylococcus aureus* and *Enterococcus*. These two infectious bacteria have developed resistance to antimicrobials which is one potential reason that Staph infection rates have increased significantly in the past decade [13]. European countries have already taken action to slow the development of resistance, removing avoparcin from their animal feed in 1997 [14]. Despite the best efforts by governments to slow this process, antibiotic resistance in oral bacteria seems to be an unavoidable end with new research indicating that in addition to exposure to pesticides, the process of aging itself correlates to an increased resistance exhibited in certain oral bacteria [15].

The final factor that impacts the oral microbiome is lifestyle. Because of the dynamic nature of the oral microbiome, short term changes in factors such as body temperature, neurotransmitter levels, and respiratory rates can account for fluctuations in bacterial richness. One experiment performed by Kupchak et al. in 2017 investigated the impact that completing a 164-km cycling event had on the types and quantities of bacteria present [16]. They found that while there was no significant change in diversity, the abundance of certain types fluctuated, specifically an increase of *Firmicutes* and a decrease in *Bacteroidetes*. The bacterial phylum *Firmicutes* have been extensively studied and it is well documented that individuals with diabetes tend to have higher abundance of this phylum compared to other oral microbiota [17]. However, it is undetermined as to whether this increase of *Firmicutes* is a potential cause of diabetes or just a by-product of the disease. Another key factor relating to lifestyle is oral

hygiene. Although extensive work has yet to be performed on this topic, research like this provides viable evidence that lifestyle plays a much larger role than we once thought.

Health Benefits of the Natural Oral Microbiome

There can be a negative connotation associated with oral bacteria, suggesting that the roles they play are all negative. However, there have been recent ideas that describe humans as a supraorganism which is made up of both the human body and its microorganisms [18]. Rather than viewing all these bacteria as parasites feeding off their human host and causing disease, we should instead consider some of them as symbiotic maintainers of our homeostatic state. A few of these benefits of microbiota include immunological priming, down-regulation of excessive pro-inflammatory responses, regulation of gastrointestinal and cardiovascular systems, and colonisation by exogenous microbes [19].

Microbiota play an essential role in the development of adaptive immunity. The human immune system is under constant exposure to outside viruses, bacteria, and other pathogens that could cause sickness and immune responses. Humans and the microbiota in the oral cavity have evolved together in service for each other. These bacteria, like any other bacteria that humans come in contact with, have the potential to elicit an immune response [20]. However, because the human body has adapted to accommodate this microbiota, no such response is shown in healthy individuals. This idea is reinforced in a study where patients with primary immunodeficiencies (lacking in their well adapted immune system) suffered from infections caused by common microbiota found in human skin and mucosal microbiome [21]. Extensive research has been done on the microbiota present in the gut and its specific effects on immunity. One example discusses the interaction of bacteria with Th17. These cells are essential in the production of IL-17 a key part of the proinflammatory response [22]. The adhesion of specific gut microbes to intestinal epithelial cells is a cue for the induction of Th17 cells, and thus of the eventual immune response cascade [23]. Although less extensive work has been performed pertaining to the oral microbiome, it is plausible to suggest that similar response pathways can be triggered via bacteria in the oral cavity, and future studies will undoubtedly bring this idea to fruition.

The formation of biofilms along the gingiva in the mouth exemplify the competitive exclusion principle seen in population biology. This principle states that two species competing for the same limiting resource cannot coexist at constant population values. Therefore, biofilms of microbiota are taking up space that other potential bacterial tenants would need to colonize [24]. For this reason, the coevolved bacteria act as a force field preventing dangerous bacteria from taking up residence in our bodies. Additionally, the native bacteria *S. mutans* has been found to produce peptides that inhibit the biofilm formation of *Candida albicans*, a pathogen that could potentially cause oral fungal infections [19]. In this way, the microbiota not only act as a physical barrier, but also a chemical one (Table 1).

Historically speaking, the commensal bacteria in the oral cavity were well adapted to the diets of ancient humans, allowing for the effective digestion of meals. Bacteria in the phylum *Ruminococcaceae*

Table 1: Health benefits associated with a healthy oral microbiome.

Health Benefit	Reference	Year	Journal
Immunological Priming	Smeekens et. al.	2014	J. Innate Immun.
	Nishio et. al.	2015	Proc. Natl. Acad. Sci. U.S.A.
Physical Barrier	Marsh	2012	Brit. Dent. J.
Chemical Barrier	Brestoff & Artis Marsh et. al.	2013	Nat. Immunol.
		2015	Caries Res.
Digestion Regulation	Duncan et. al.	1995	Nat. Med.

were associated with good health and were found in high frequency [5]. Unfortunately, these well adapted bacteria are present in much lower frequencies in humans today, most likely due to our change in diet. Research is still being performed to determine current roles that high frequency bacteria play in digestion, although it is suspected to be large. The bodies first line of breaking down carbohydrates comes in the form of salivary amylase. This liquid is made up of digestive enzymes in addition to a few other chemicals. Recent findings show that in addition to the body’s natural digestive enzymes, the commensal bacteria aid in the digestion including extraction, synthesis and absorption of many nutrients and metabolites [25]. One such case is the reduction of nitrate to nitrite. This is carried out by anaerobic bacteria through the production of nitrate reductase enzymes [26]. This nitrite will subsequently play a key role in cardiovascular health, acting as a strong vasodilator and antimicrobial agent. More generally, bacteria all along the gastrointestinal tract have been associated with the production of bile acids which are important factors in the digestion of fatty acid chains [25]. While research is still examining more specific roles of modern day oral bacteria, it is likely that they have continued to co-evolve with us humans as our digestive needs have shifted.

The Oral Microbiome and Disease

Despite the coevolution of these bacterial species and their numerous health benefits, modern diets and dental habits have greatly impacted the oral cavity and an influx of negative bacteria have claimed the territory as their home. The increased exposure humans have to heavy metals, disinfectants, and antibiotics have led to the positive selection of bacteria with resistances to such compounds [27]. While not all these newly adapted bacteria brought an onset of dental problems, a significant number did such as *Streptococcus mutans* being able to outcompete other oral bacteria species and becoming one of the leading causes of tooth decay [28]. Oral and periodontal diseases (caries, chronic and aggressive periodontitis, mucositis, and gingivitis) are associated with changes to the microbiome, specifically

prevalence of anaerobic bacteria within the flora [29]. Most diseases are rarely caused by a single bacterium, but rather a combination of species or complexes.

Gingivitis simply refers to the inflammation of the gum tissue. It tends to be acute and fairly manageable. However, left untreated, it can progress to later stages called periodontitis where the inflammation reaches the bone and soft tissue associated with anchoring the teeth resulting in the eventual loss of teeth [30]. The primary cause for such diseases can be traced to a complex of bacteria referred to as the ‘red complex’. This complex is made up of *P. gingivalis*, *T. forsythia*, and *T. denticola* [11]. While other bacteria can be linked to these diseases, it is the red complex that is most often associated with the onset. The red complex tends to appear in later stages of biofilm development, suggesting that earlier bacterial species, referred to as keystone pathogens, will impair the immune response of the host and prepare a habitat for the red complex to eventually succeed [31]. While the red complex works as a unit, research has linked high amounts of *T. forsythia* with greater severity of lesions or pockets, and *T. denticola* with greater severity of bleeding [32] (Table 2).

Dental caries encompasses both moderate and extreme tooth decay. It is one of the most prevalent human bacterial infections and similar to periodontitis, can lead to tooth loss. In the past, *Streptococcus mutans* has been viewed as the main cause of dental caries; however, recent research has shown that not all subjects with caries have detectable levels of this bacteria, proving that there are other bacteria involved [33]. It is widely accepted that the bacteria responsible thrive under low pH conditions, since the ingestion of acidic meals can recruit these bacteria. Interestingly enough, there seems to be a socioeconomic distinction about what bacteria are responsible in each individual. In a comparative study between Romania and Sweden it was found that in Romanians with dental caries where dental health care is uncommon, seemed to be infected with the classic. *S. mutans* and *S. sobrinus*. Alternately, in Sweden where dental health care is more widespread, individuals with dental caries were infected with other bacteria such as *Actinomyces*, *Selenomonas*, *Prevotella*, and

Table 2: Common oral / periodontal diseases and associated bacterial species.

Disease	Associated Bacteria	Reference	Year	Journal
Gingivitis	<i>Porphyromonas gingivalis</i>	Socransky et. al.	1998	J. Clin. Periodontol.
	<i>Tannerella forsythia</i>			
	<i>Treponema denticola</i>			
Tooth Decay	<i>Streptococcus mutans</i>	Cornejo et. al.	2013	Mol. Biol. Evol.
	<i>Streptococcus mutans</i>	Salman et. al.	2017	Contemp. Clin. Dent.
Dental Caries	<i>Streptococcus sobrinus</i>			
	<i>Actinomyces</i>	Johansson et. al.	2016	J. Dent. Res
	<i>Selenomonas</i>			
	<i>Prevotella</i>			
	<i>Capnocytophaga</i>			

Capnocytophaga [34]. Possible explanations for the disparity could include diet as well as hygienic habits. This research suggests that tooth decay is a common problem in all humans, though the bacteria responsible may be contextually unique.

In addition to the oral diseases, the oral microbiota has been linked to neurodegenerative diseases. Diseases such as periodontitis and dental caries previously discussed can stimulate an inflammatory response in the body, eventually leading to low-grade systemic inflammation [35]. This inflammation can easily travel to the blood vessels, which have been previously shown to have a significant role in the pathogenesis of neurodegenerative disease. As discussed earlier, mounting evidence suggested that the blood brain barrier (BBB) is inadequate to protect the brain from circulating infectious bacteria from the oral cavity. Moreover, upon entry to the brain, oronasal and periodontal bacteria do not elicit the normal inflammatory responses such as meningitis and encephalitis to a noticeable degree to the host body, and therefore the accumulation of neuronal insult, as well as the natural onset of immunosenescence leads to the prevalence of age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, associated with oral and periodontal disease-related bacteria.

Normal oral bacteria metabolize components of the food that we eat and release compounds that are then absorbed into the bloodstream. This metabolism-based relationship between the bacteria and the host requires a significant amount of immune tolerance on the part of the host to bacterial secretions. The tolerance provided by the host, however, presents a substantial risk to bacterial entry to the bloodstream and subsequent translocation to body areas where oral bacteria would be detrimental to the surrounding environment. Additionally, mounting evidence has shown that protective barriers, of particular importance to this review, the Blood-Brain Barrier (BBB), are inadequate to prevent this spread of bacteria, leading to significant risk of neuronal insult from oral and periodontal diseases.

Potential Pathways that Influence Spread

Van Velzen, Abraham-Inpijn, & Moorer published a review in 1984 in which they determine three mechanistic links between bacterial load increase due to periodontal and oral disease and systemic diseases elsewhere in the body, otherwise known as focal infection [36]. Each pathway presents a potential initiating factor for circulation of oral bacteria throughout the body, leading to its deposition in distant organs. These three pathways are:

1. Metastatic infection due to transient bacteremia
2. Metastatic inflammation due to immunological injury
3. Metastatic injury due to microbial toxins

It should be noted that there may be other substantial mechanisms of focal infection, but research has not illuminated these pathways yet.

Metastatic Infection

Metastatic infection is the most documented and best-understood pathway of focal infection and describes the spread of oral microbes throughout the body as a direct result of bacteremia. As discussed above as the blood circulation pathway of spread, bacteremia is typically caused by normal dental hygiene practices such as brushing

and flossing in patients with periodontitis or other oral diseases. Likewise, oral surgery, such as root canals, have also been shown to cause transient bacteremia [37].

In a healthy human, a small amount of transient bacteremia does not result in long-term systemic inflammation and is usually cleared by the body within 1 hour of spread. However, if the bacteria find favorable conditions, such as in the brain, heart, or lungs, large densities of bacteria tend to localize and begin multiplying. Particularly, a majority of oral microbes have developed the ability to strongly adhere to the surfaces of other cells and tissues, an ability necessary for survival in the tumultuous environment of the oral cavity, and present a significantly increased risk of localization when introduced to the bloodstream.

Metastatic inflammation

There are numerous substances that are able to pass through the epithelial barrier and enter the bloodstream, and plaque in the oral cavity is one such substance. The rate of crossover, particularly in the gingival sulcular lining of the oral cavity, is dependent on the size of the molecules, but can also be accelerated by chronic inflammation of the gums. Therefore, inflammation caused by plaque buildup in the mouth both presents substantial risk of toxic bacteria to spread throughout the body, and also acts to facilitate the spread through chronic inflammation of the oral lining.

In addition to the inflammatory response to plaque in the oral cavity, oral microbes also elicit an inflammatory response due to shared antigens with the host body. As part of the adaptive immune response to bacterial infection, a host body will release antibodies specific to highly-conserved antigens of the infected bacteria. However, the host body often shares a number of the same antigens that are targeted by secreted antibodies, thereby causing autoimmune damage, particularly to the tissues surrounding an area of antibody localization, and allowing bacterial entry to the bloodstream. Such self-destructive antibodies are referred to as cross-reacting antibodies and present a substantial risk to bacteremia in response to complement activation.

In conjunction with autoimmune damage caused by secreted antibodies, in some cases where blood borne antigens outnumber circulating antibodies, intravascular antigen-antibody reactions occur that cause the formation of macromolecular complexes that continue to circulate throughout the body. As such immune complexes circulate, they can begin to localize and deposit throughout the body and cause acute and chronic inflammatory side effects, increasing the likelihood of bacterial deposition into distant organs from the mouth.

Metastatic injury

Microorganisms produce toxins, such as LPS, that exert significant stress on surrounding tissues and cells. These toxins appear to be the major cause of most neuronal damage that occurs as a direct cause of an unhealthy microbiome. Most often neuronal injury begins in the periphery from circulating bacteria in the blood. The current consensus follows that bacterial toxins target the myelin sheaths of peripheral neurons. Chronic neuronal stress from bacterial endotoxins can then move to the trigeminal ganglion neurons before eventually affecting significant neuronal changes throughout the

central nervous system. As proof of concept, Ratner et. al. showed in 1979 that pain experienced by patients with idiopathic trigeminal or atypical facial neuralgia was closely related to maxillary or mandibular bone cavities at the sites of previous tooth extractions where they discovered a diverse flora of aerobic and anaerobic microorganisms [38]. This funding directly implemented the oral microbiome in external symptoms of a nervous system related disease.

Beyond the Mouth: 4 Hypotheses of Entry Sites to the Brain

Shoemark & Allen (2015) describe four potential pathways that oral bacteria use to enter the brain [39]:

1. Blood Circulation
2. The Blood-Brain Barrier
3. The Olfactory Hypothesis
4. Circumventricular Organs and Perivascular Spaces

Each of these four pathways have been implemented in neuroinflammation leading to neuronal damage. It is currently unclear if one of these pathway is more prevalent than the others, but it is clear that each of these pathways has been observed in the spread of harmful bacteria associated with periodontal disease.

Blood circulation

During oral and periodontal diseases, the infectious burden begun in the mouth presents a substantial burden to the rest of the body, due to the easy spread to the rest of the body from the mouth. Additionally, certain microorganisms release highly toxic LPS alongside the cytokine release that may enter the bloodstream during the inflammatory response. Likewise, daily dental hygiene treatments such as brushing, chewing, flossing, and using toothpicks introduce small cuts in the gums and oral lining allowing bacteria to enter into the bloodstream, a condition known as bacteraemia. This crossover event presents significant risk to patients with periodontal diseases by providing harmful anaerobic bacteria a pathway into the bloodstream. In fact, patients with periodontitis exhibit bacteraemia multiple times a day, and bacteria have been shown to persist in the bloodstream for upwards of three hours [2]. Moreover, after spreading to vascular channels, bacteria have the capacity to spread throughout the body to the heart, brain, and lungs within one minute.

The blood-brain barrier

The endothelial cells lining the blood capillaries are held together by tight junctions forming a nearly impenetrable barrier to circulating blood toxins and bacteria. However, chronic inflammation caused by periodontal disease-related bacteria can weaken the BBB, allowing easier access to the brain by harmful bacteria. Additionally, the normal aging process causes tight junctions at the BBB to loosen, allowing easier crossover into the brain by bacteria that may cause subsequent neuronal stress and damage. Compounded over the lifetime, this neuronal stress can lead to age-related neurodegeneration and cognitive decline [39].

Circumventricular organs and perivascular spaces

The Circumventricular Organs (CVO), such as the pineal gland,

are structures that allow hormones from the hypothalamus to exit the brain without disrupting the BBB, and are essential to efficient and proper secretion of hormones throughout the body. Additionally, the CVOs also function in shuttling substances secreted by organs elsewhere in the body that would normally not cross the BBB to enter the brain to enact neuronal changes in response to stimuli from the periphery. On top of the CVOs, Perivascular Spaces (PVSs) filled with circulating interstitial fluid that surround the vesicles, also present easier access to the brain for bacteria than an intact BBB [39].

The Olfactory hypothesis

Many nerves connect the oronasal cavity directly to the brain, specifically the trigeminal and olfactory nerves. Previous research has shown that the trigeminal nerve is capable of sustaining measurable levels of bacteria of the phylum Treponema, a class of obligate anaerobes that have been implemented in the development of multiple diseases [40]. Additionally, Olfactory Ensheathing cells (OECs), the typical line of defense against bacterial infection along the olfactory tract, have been shown to be inadequate to prevent the crossing over of bacteria, such as *Staphylococcus aureus* [41]. Moreover, OECs have been used to administer nanoparticle drugs to the brain, showcasing its ability to bypass the BBB entirely [42].

Proposed Mechanisms of Neurodegeneration

Knowledge of the pathways used by oral pathogens to spread to distant organs presents only one facet of the bacterial role in development of neurodegenerative diseases. Spirochetes, an obligate anaerobic bacteria associated with periodontal disease has been implemented frequently in the literature examining bacterial effects on neurodegeneration. In general, spirochetal infection activates immune signaling pathways such as toll-like receptor signalling and the complement cascade. As these pathways progress, the intermediate products of these pathways mediate the inflammatory response to bacterial infection, and are often used as biomarkers for central nervous system inflammation. As part of the natural immune response, activation of both the innate and adaptive immunities results in the production of free radicals and apoptosis of infected cells [29]. When present in chronically elevated amounts, bacterial presence can lead to immune cell exhaustion, as well as overproduction of free-radicals and excessive apoptosis, which will be discussed later as prominent mechanisms of bacterial-induced neurodegeneration. Specifically, the periodontal disease bacteria *Porphyromonas gingivalis* has been shown to elicit the inflammatory response described above, but additionally possesses the ability to elude immune factors and sustain chronic inflammation over long periods of time [43]. Therefore, upon entry into the brain by one of the previously described pathways and mechanisms, *P. gingivalis* induces chronic inflammation leading to neuronal damage. Depending on the extent of neuronal damage, the presence of *P. gingivalis* in the brain may be quickly detectable by outward symptoms or may amass over the lifetime and become evident only in elderly patients. This variability explains the observation of *P. gingivalis* prevalence in both trigeminal and atypical neuralgias, as well as in age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.

More specifically, bacterial spread to the nervous system induces neurodegeneration in two ways: production of free radicals in the

form of reactive oxygen species and reactive nitrogen species, and secretion of endotoxins in the form of endogenous neurotransmitters secreted in excess. As with most systemic damage, neurodegeneration begins at the cellular level with these two pathways, and subsequent cell death causes the spread and intensifying cell damage leading to the measurable changes in neuron density and observable changes in neurocognition. Each of these pathways will be looked at more in depth below.

Formation of free radicals leading to neurodegeneration

It is well documented that bacterial cell wall components, particularly LPS, are highly resistant to mammalian enzymes and degradation pathways, and therefore allow bacteria to induce long-term infection, and a chronic inflammatory response mediated by cytokine release. Along with chronic systemic inflammation, cell wall components of infectious bacteria also induce the formation of free radicals within infected cells [44]. Free radicals, in elevated levels, are sufficient to cause cell membrane damage as well as damage to mitochondrial DNA. The effects of membrane and mitochondrial damage than cause infected cells to die and undergo apoptosis, thus releasing free radicals trapped inside the infected cell to cause further damage to surrounding cells.

Excitotoxic release of endogenous neurotransmitters leading to neurodegeneration

In the normal processes of neuronal activity, excitatory neurotransmitters, such as glutamate and homocysteine, act to promote the firing of action potentials and the propagation of information throughout the nervous system. However, due to the damage to mitochondrial DNA as discussed above by free radicals, cellular energy as a whole decreases and neurons become significantly more sensitive to small amounts of excitatory neurotransmitters. Under these conditions, even basal levels of excitatory neurotransmitters can lead to overstimulation of neurons and neuronal exhaustion from excessive firing. This leads to the the activation of the p53 gene within overstimulated and exhausted neurons that signals to the neuron to undergo apoptosis. Therefore, the free radical mechanism discussed above induces a systemic response by depleting neuronal energy and causing proliferation of p53 gene proteins. Accumulation of neuronal damage and cell death overtime due to chronic infection and over-sensitization of neurons to stimulation evidences the link between spread of microbes from the oral cavity with progressive neurodegeneration.

Potential Diseases Caused by Spread of Harmful Oral Bacteria

The spread of harmful pathogens from patients with periodontal disease has been associated with multiple kinds of systemic infections and diseases. For example, The oral microbes *A. actinomycetemcomitans*, *P. gingivalis* [45], *Porphyromonas gingivalis*, *Treponema denticola*, *Cytomegalovirus* and *Chlamydothyla pneumonia* [46] have all been implemented in the development of atherosclerosis, all of which are anaerobic microbes. A recent study found that prolonged periodontal treatment and changing of oral hygiene habits decreased oral anaerobes, reduced inflammatory biomarkers, and reversed thickening of the carotid artery associated with atherosclerosis [47]. However, for the purposes of this review,

the following section will focus on the neurodegenerative diseases Alzheimer's and Parkinson's disease, and the role oral pathogens play in their development using the neurodegenerative mechanisms described above.

Alzheimer's disease

Alzheimer's disease is the most common form of dementia. Symptoms include loss of ability to form new memories leading to confusion, and eventually inability to self-care requiring institutionalization. Typical age of onset in America is 85 to 89 years old, but early cases have become more common in recent history.

Evidence for an inflammatory response within the AD brain

Specifically, astrocyte-mediated inflammation evidenced by increased levels of inflammatory cytokines (TNF α IL-1 β). In 2009, researchers showed that blood levels of TNF α and antibodies for oral bacteria were significantly higher, as much as 6 times higher, in Alzheimer's patients compared to controls. This discovery has lead to analysis of how these abnormal serum levels might be used as a diagnostic tool, further evidencing the crucial role the oral microbiome is playing in the spontaneous pathogenesis of Alzheimer's disease [48]. Miklossy (2011) found that oral bacteria were present at a 7-fold increase and with more variety in AD brains than normal control [49]. Specifically, AD brains contained a large number of oral spirochetes, obligate anaerobes from the phylum Treponema (Table 3).

The Swedish Twin Registry, begun in the 1950s, found a significant correlation between dementia and tooth loss before the age of 35 [50]. This was duplicated in a study of North American Nuns [51]. These correlations assume that early tooth loss is indicative of poor oral hygiene, and rely on this assumption to evidence the role of the oral microbiome in these findings.

Additionally, the AD11 mouse model of Alzheimer's disease has been shown to produce antibodies which sequester nerve growth factor throughout their lifetime. This decrease in basal levels of an essential growth factor slowly removes the support necessary for proper development of cholinergic cells in the basal forebrain, leading to the hallmark symptoms of impaired memory, amyloid-beta and hyperphosphorylated tau lesions, and loss of cholinergic basal forebrain neurons. Important to this review, when the AD11 mouse model is raised in sterile conditions, the onset of observable neuropathological changes and cognitive impairment is delayed [52].

It is unclear whether the oral bacteria themselves or secreted endotoxins, such as LPS, are entering the brain in the pathogenesis of Alzheimer's disease. What is clear, however, is that regardless of in what form the bacteria are exerting their effects on neuronal stress, the outcome will be microglial activation, specifically of astrocytes, and the subsequent elevation of TNF α and IL-1 β as discussed above. This claim is also strengthened by the recent discovery that amyloid beta oligomers, while neurotoxic to the surrounding environment, also exhibit intrinsic antimicrobial capacity and may reflect an evolutionary adaptation of the human brain to fight off bacterial infection [53]. This suggests that elevated bacterial load in the brain may be the triggering factor leading to elevation of amyloid beta oligomers and subsequent neurotoxicity from the aggregates left over

Table 3: Associations between oral cavity and neurodegenerative disease.

Finding	Reference	Year	Journal
Alzheimer's Disease			
Correlation between AD and tooth loss	Gatz et. al.	2006	<i>Alzheimers Dement.</i>
	Stein et. al.	2007	<i>J. Am. Dent. Assoc.</i>
Aβ has intrinsic antimicrobial capacity	Soscia et. al.	2010	<i>PLoS ONE</i>
8-fold elevation of spirochetes in AD patients	Miklossy J	2011	<i>Expert Rev. Mol. Med.</i>
AD11 mice raised in sterile environment delays cognitive impairment	Capsoni et. al.	2012	<i>J. Alzheimer's Dis.</i>
Parkinson's Disease			
Linkage of caries, periodontal disease, and tooth loss with PD	Müller et. al. [57]	2011	<i>Spec. Care. Dentist.</i>
Elevated levels of opportunistic microbes in PD patients	Pereira et. al.	2017	<i>Parkinsonism Rel. Disord.</i>

after the infection has been cleared.

Taken together, this evidence seriously implements the oral microbiome on the pathogenesis of Alzheimer’s disease. Furthermore, as humans age, the bacterial load present in the body naturally increases due to immunosenescence, and the specific microbiome composition of an individual is becoming increasingly important for lifelong health. As the human body ages, the innate immune system predominates the anti-infectious response, and the threat of increasing bacterial load from unchecked microbiomes intensifies the importance of maintaining the innate immune barriers, such as the BBB. This push-and-pull relationship established by early or chronic periodontal and oral diseases predisposes the aged immune system to succumb to breach of damaging bacteria, thus accelerating the accumulation of amyloid beta and amplification of neurocognitive deficits associated with the Alzheimer’s disease.

Parkinson’s disease

Parkinson’s disease is an age-related neurodegenerative disease associated with loss of dopaminergic neurons in the substantia nigra, as well as the presence of α-synuclein deposits throughout the brain. Typical outward symptoms of Parkinson’s disease are bradykinesia, rigidity, and tremors. However, research has not fully illuminated the exact neuropathological mechanism that leads to the onset of Parkinson’s disease, but current hypotheses center around the roles α-synuclein oligomerization, oxidative stress, and mitochondrial dysfunction. Interestingly, each of these potential risk factors for Parkinson’s disease have been previously shown to be linked to transient bacteremia of anaerobic microbes from the oral cavity and other microbiome localizations. Therefore, it is likely that the proposed mechanisms of bacterial spread discussed in the previous sections of this review present potential monitorable early risk factors for development of Parkinson’s disease [54].

Multiple projects in the development of Parkinson’s disease have involved neuroinflammatory processes, however further research into the benefits of anti-inflammatory drug treatment have yielded mixed results [54]. This may be due to a lack of understanding and in-depth analysis of the kinds of anti-inflammatory drugs tested, and so discrepancies in current research need to be examined more closely. Most surely, the current body of research relating neuroinflammatory processes to Parkinson’s disease should not be considered extensive, and present numerous additional outlooks that must be explored. To be clear, however, neuroinflammation does not appear to be the primary cause of cell death in Parkinson’s disease, dissimilar to Alzheimer’s disease or other neurodegenerative diseases, but instead presents what can be thought of as a side-effect of the primary

pathogenesis of Parkinson’s that acts as a catalyst to accelerate the deficits characteristic of the disease.

Interestingly, endogenous pathological antigens have been implemented in the activation of both the innate and adaptive immune system. As previously described in this review, antigen presence in the body can elicit damage to the surrounding environment by either cross-reacting antibodies and intravascular antigen-antibody complexes. Therefore, it is no stretch to hypothesize that transient bacteria gaining access to the brain could induce neurodegenerative effects through one of these two mechanisms [54]. In fact, when compared to normal human oral microbiome diversity, the oral microbiomes of Parkinson’s patients displayed elevated levels of opportunistic microbes, particularly of the phylum Treponema, the obligate anaerobes implemented in several other neurodegenerative disorders [55]. However, a substantial analysis of bacterial load of a Parkinson’s brain has not yet been performed, and therefore the current body of data lacks evidence of microbes associated with the oral cavity or periodontal disease. However, current research points to the significant potential that periodontal-disease related bacteria will be present in higher densities in the Parkinson’s brain.

Looking to the future, further knowledge of the microbiomes present within the human body, as well as their interactions with the human genome, will improve both the validity of diagnosis of neurodegenerative diseases, as well as provide potential risk factors that can be used for early prediction and attenuation of symptoms prior to the current clinically diagnosable onset. Furthermore, accumulation of data on these interactions will accelerate the clinical research into candidate drugs and therapies to aid in the treatment of neurodegenerative diseases.

Concluding Remarks

While microbiota tend to have a bad reputation, and there is substantial research outlining the plethora of harmful infections that can be caused by rampant spread of this bacteria, it is important to remember that humans and bacteria have coevolved ever since the dawn of humanity. The connection we share is complex and is clearly both good and bad depending on the type, prevalence, and location of these bacteria. To dictate that the microbiota housed in our bodies are entirely commensalistic or even parasitic would neglect this relationship that we have developed. While the roles of some bacteria remain unknown and the degree to which some may cause neurodegenerative diseases requires further research, their importance to maintaining human life is evident and must not be forgotten.

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ISSN: 2377-987X

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