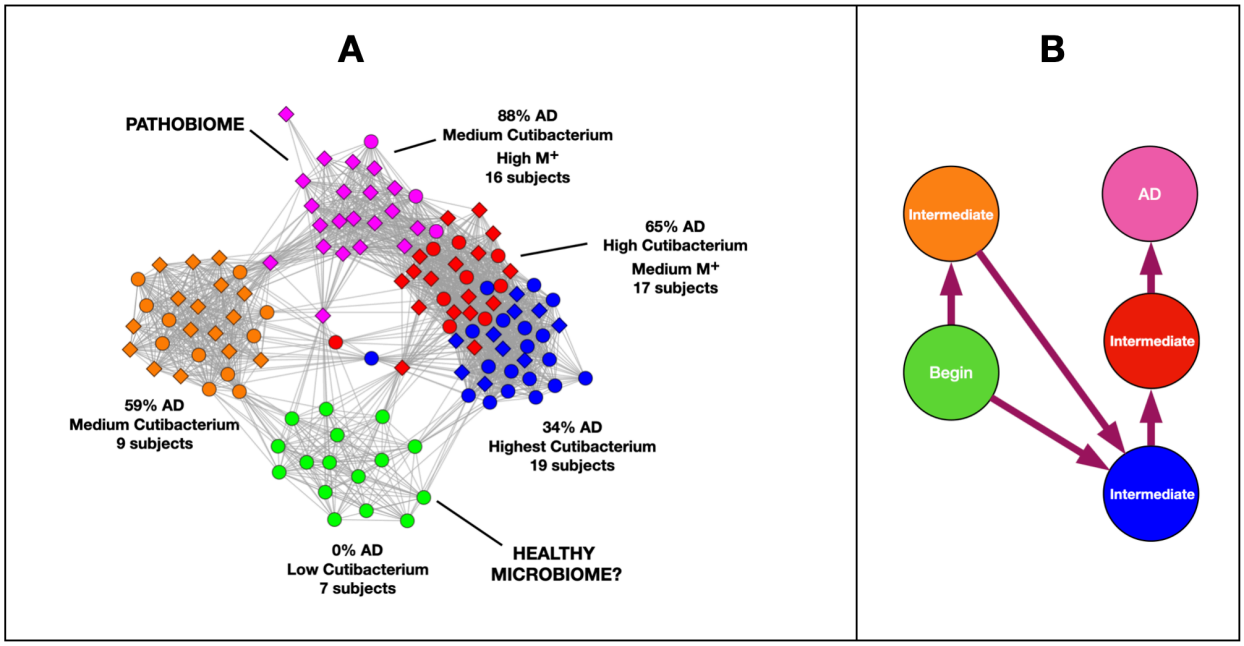
Evidence for a Microbial Basis for Alzheimer's Disease

Introduction. We believe we have made major breakthroughs in understanding Alzheimer's disease (AD) as an infectious illness caused by microbes: bacteria, fungi, parasites or viruses. Specifically, we have found evidence of a bacterial role. Our Alzheimer's group conducts research at Drexel Univ. College of Medicine, Dept. of Microbiology and Immunology. We are building an international research coalition working on various aspects of this idea.

Background. Since the neurological illness, Alzheimer's disease, was first described over a hundred years ago, researchers have conjectured that microbes are involved. With over 6 million Americans affected and no broadly-accepted treatment, establishing a general microbial trigger would create new possibilities for treatment, perhaps with approved medications.

The microbial hypothesis has received little attention in recent decades. Instead, research and drug development has focused on interrupting processes seen in AD brains: amyloid beta (Aβ) plaque deposits between brain cells and protein abnormalities called neurofibrillary tangles observed in brain cells. Drugs resulting from this research are not very effective. The discovery, however, that amyloid plaques have anti-microbial activity strongly suggests that the brain creates them in response to bacterial infection. Epidemiological observations that certain vaccinated groups have a lower incidence of AD further supports the idea.



A. Graph of samples (~4/brain). Circular nodes are samples from controls and diamonds are from Alzheimer's (AD) subjects. The color represents the type of microbiome. Nodes are placed near one another if their bacterial content is similar. Edge lines are drawn when the similarity reaches a predefined threshold. Annotations indicate: (i) fraction of color cluster from AD subjects, (ii) qualitative abundances of *Cutibacterium acnes*, and (iii) number of subjects with samples in color cluster. The axes do not have biological meaning, only the nearness of nodes. **B.** Time evolution of microbiomes beginning with a possibly healthy microbiome proceeding to the pathobiome using the same colors as A.

Ongoing Research. There are several research groups around the world that have been looking at the infectious hypothesis, including our Drexel group. We have been studying the post-mortem brains of elderly AD patients and non-AD brains for comparison with a focus on bacteria. We used an advanced form of genomic sequencing, pioneered in our labs, to identify bacteria and machine algorithms adapted for bacterial communities. Our findings were recently accepted for publication in a peer reviewed journal.

Microbiome Evolution. Interestingly, we found bacteria in both cohorts, often the same bacteria, making it difficult to identify any pathogenic patterns. Using the machine learning, however, we were able to group the bacteria into several distinct sets of bacteria, microbiomes, that appeared to have different roles in the illness.

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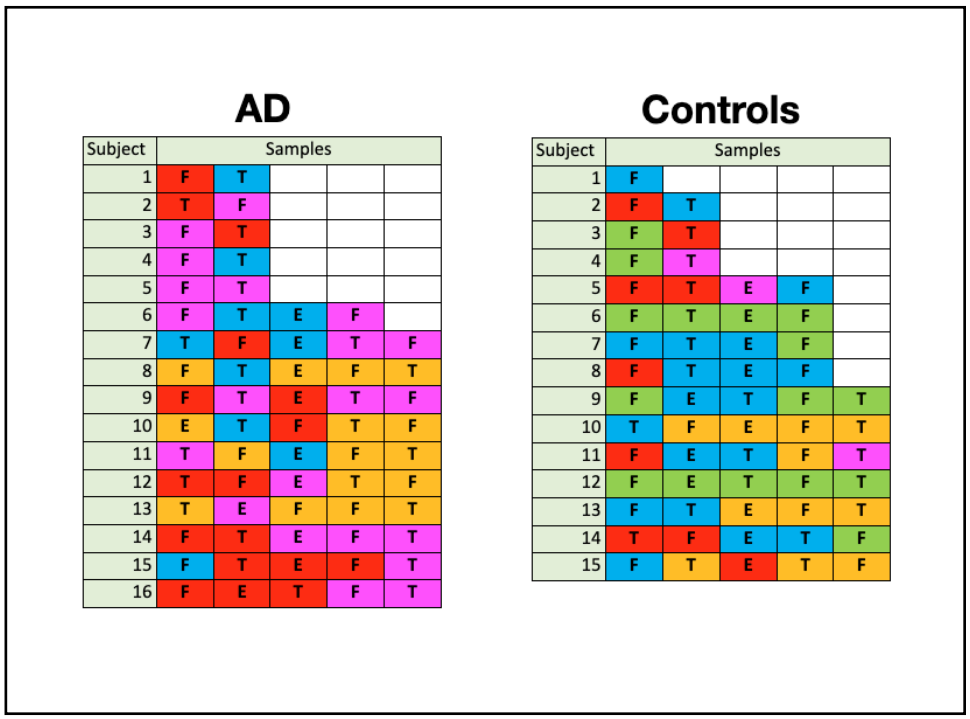
These microbiomes occurred at different times during the evolution of the disease beginning with a healthy microbiome and evolving into a pathogenic microbiome, the pathobiome. This finding suggests that there is a physiological change in the brain that allows different bacteria with varying abundances to flourish at different times.

We found that the healthy microbiome that only occurred in the controls disappeared at an early stage, perhaps heralding disease onset. Next came a set of intermediate microbiomes that were not correlated with the cognitive deficits of AD. It could be that plaques develop in response to these microbiomes, possibly explaining the medical fact that plaques occur in both AD and non-AD subjects. Last, the microbiome evolved to the pathobiome, that was nearly exclusively found among AD subjects.



Each cell represents a sample and each row is a subject. Cell color is the type of microbiome with sample location designated by F: frontal lobe, T: temporal lobe, and E: entorhinal cortex. The magenta class is the pathobiome containing *C. acnes, , Methylobacterium.* and others. Inspection indicates that most of the AD subjects contain the magenta microbiome. The green class might be a healthy microbiome dominated by *Comamonas*. The red, blue and orange classes have no strong correlation with AD. They may represent early-stage infections that induce plaque and tangle formation prior to development of cognitive deficits.

The Pathobiome. There were usually two dominant bacteria occurring in samples containing the pathobiome. One of the members of this pair was a skin bacterium called *Cutibacterium acnes* (formerly *Propionibacterium*, *C. acnes)*, an acid producing bacterium that is unable to move by itself. It is ubiquitous, occurring in both AD and controls subjects, suggesting it is not pathogenic.

The other member of the pair was from a set of bacteria that are often found in soil and aquatic environments, i.e., everywhere (called M+ since one is *Methylobacterium*). Some can move unaided and some cannot. The crucial question that this pairing raises is whether the pathobiome derives its pathogenicity only from the M+ as the *C. Acnes* were already there when the M+ arrived. Alternatively, some form of interaction between the two may account for its pathogenicity, such as *C. acnes* creating an acidic environment for M+ to flourish although there are numerous other scenarios. A similar set of bacteria has been found in the motor cortex of ALS subjects containing *Methylobacterium* and *C. Acnes*.

It is compelling that, even though we analyzed only a few samples per brain, this pathobiome was found in almost all AD subjects and almost no controls. **See figure above.**

Last, our results were consistent with the bacteria being delivered over large areas of the brain through one or more of the brain's vascular, lymphatic or nervous networks. This delivery mechanism could explain the presence of bacteria that cannot move on their own. More importantly, the gradual failure of these networks may allow different bacteria to leak into the brain at different phases, partially accounting for the different microbiomes we observe at different times. Immunological and genetic factors are likely important too.

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Next Steps. It is of paramount importance to understand the microscopic structure of the pathobiome because this has the potential to explain the mechanisms of its pathogenicity. Advanced microscopy can reveal the location of the different types bacteria and their positions inside of cells, between cells, within and beyond the brain's networks. We also plan to expand our investigation to include eucharioticmicrobes such as fungi and parasites and also viruses. We will study younger subjects to confirm the existence of the healthy microbiome and explore interactions between microbes in vitro that might provide clues for why it disappears and what might account for the pathobiome's properties.

Concluding Thoughts. It is improbable that the observed microbiome composition and dynamics occurred by accident. On the contrary, these findings call out for explanation in fundamental terms. It is a complex dynamic that likely involves the time dependence of multiple interacting systems: including the microbial ecosystems, a changing immune reaction with genetic constraints, and dynamic failing delivery networks driven by external factors that could have happened once or are ongoing. This investigation has only begun to uncover how this works. Understanding AD apparently will involve a program of examining these fundamental components, how they affect each other and ultimately how they affect the function of the mind.

In a field that has no answers for millions of afflicted people afflicted with Alzheimer's, the idea that microbes are involved in the illness now has substance. It is generating testable conjectures, propelling it from mere observation toward the discovery of disease mechanisms and treatments.

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