The hidden cause of disease

Everything from heart disease to Alzheimer's has been blamed on unhealthy lifestyles. But could pervasive bacteria be the true culprits, asks **Debora MacKenzie**

FOR decades, health experts have been lecturing us about our bad habits, blaming them for the surge in "lifestyle diseases". These often come on as we age and include heart disease, Alzheimer's, type 2 diabetes and some cancers. Worldwide, 70 per cent of all deaths are now attributed to these conditions. In the UK, it is a whopping 90 per cent.

Too much red meat, too little fruit and veg, smoking, drinking, obesity and not enough exercise appear to make all these diseases more likely – and having any of them makes getting the others more likely. But no one really knows why, and we still haven't worked out what causes any of them. Alzheimer's is now one of the UK's biggest killers, yet the main hypothesis for how it originates imploded this year after drugs based on it repeatedly failed. High blood cholesterol is blamed for heart attacks, except most people who have heart attacks don't have it.

What we do know is that these conditions usually start causing symptoms later in life, and their prevalence is skyrocketing as we live longer. They all turn inflammation, the method our immune system uses to kill invaders, against us. And, by definition, these diseases aren't communicable. They are down to bad habits and unlucky genes, not germs. Right?

Not necessarily. In disease after disease, we are finding that bacteria are covertly involved, invading organs, co-opting our immune systems to boost their own survival and slowly making bits of us break down. The implication is that we may eventually be able to defeat heart attacks or Alzheimer's just by stopping these microbes.

Until now, bacteria's involvement completely eluded us. That's because they tend to work very slowly, stay dormant for long periods or hide inside cells. That makes them difficult to grow in culture, once the gold standard for linking bacteria to disease. But now DNA sequencing has revealed bacteria in places they were never supposed to be, manipulating inflammation in just the ways observed in these diseases.

"The main hypothesis for how Alzheimer's originates imploded this year"

The findings are so contrary to received wisdom and emerging in so many diseases, each with its own separate research community, that awareness of all this is only starting to hit the mainstream (See "Germ theory", page 46). And predictably, as with any paradigm shift, there is resistance.

But some researchers, frustrated by years of failure to find causes, and therefore real treatments, for the diseases of ageing, are cautiously excited. And with reason: this could change everything.

The worst culprits, which seem to play a role in the widest range of ailments, are the bacteria that cause gum disease. This is the most widespread disease of ageing – in fact, "the most prevalent disease of mankind", says Maurizio Tonetti at the University of

Hong Kong. In the US, 42 per cent of those aged 30 or above have gum disease, but that rises to 60 per cent in those 65 and older. It has been measured at 88 per cent in Germany.

Strikingly, many of the afflictions of ageing – from rheumatoid arthritis to Parkinson's – are more likely, more severe, or both, in people with gum disease. It is possible that some third thing goes wrong, leading to both gum disease and the other maladies. But there is increasing evidence that the relationship is direct: the bacteria behind gum disease help cause the others.

Circumstantial evidence is certainly damning. In the US, states that put federal Medicaid funds towards people's dental costs, including those related to preventing or treating gum disease, ultimately pay between 31 and 67 per cent less than states that don't, to help those people later with heart attacks, diabetes, strokes and cancer. Private insurance companies report similar patterns, says David Ojcius at the University of the Pacific in San Francisco.

But how can the bacteria that cause gum disease play a role in all these conditions? To answer that, we have to look at how they turn the immune system against us.

Your mouth hosts more than 1000 species of bacteria, in a stable community where potential bad actors are kept in check by peaceful bacteria around them. Elsewhere in the body, including on the skin or the lining of the gut, communities of bacteria live on a continuous sheet of cells, where the outermost layer is constantly shed, getting rid of invasive bacteria. But your teeth can't cast off a layer like that, says Tonetti. There, the bacteria live on a hard surface, which pierces through the protective outer sheet of cells.

When the plaque the bacteria on your teeth live in builds up enough to harden and spread under the gum, it triggers inflammation: immune cells flood in and destroy both microbes and our own infected cells ›

Master of concealment

If the bacterium *Porphyromonas gingivalis* is partly to blame for a wide range of inflammatory diseases such as Alzheimer's and heart disease (see main story), why not just kill it? Unfortunately, it is brilliant at dodging our defences: lurking inside cells where antibodies can't reach it, and often lying dormant, making it invisible to antibiotics, which mostly attack bacteria as they divide.

We could vaccinate against *P. gingivalis*, but vaccines work by inducing antibodies. People with gum disease already make antibodies against the bacteria, but these seem to do little to stop it.

It may be better to have the antibodies early and stop *P. gingivalis* invading our mouths when we are young. Eric Reynolds at the University of Melbourne is running a clinical trial of a vaccine that targets gingipains, the protein-digesting enzymes that *P. gingivalis* makes. Caroline Genco of Tufts University in Massachusetts is also working on an anti-gingipain vaccine. "The key is to prevent it ever colonising," she says.

The trouble is, many of us already host the bacteria. Routine gum abrasion, through eating or brushing your teeth, can release the microbes into your bloodstream, even if you don't have gum disease. There it can spread throughout the body and promote inflammation.

In studies by the company Cortexyme, antibiotics killed *P. gingivalis* in mice, but it rapidly became resistant. To limit resistance, instead of trying to kill the bacteria, it may be better to block its ability to cause disease. Cortexyme has a drug that does this by blocking gingipains. In mice, it reversed Alzheimer's-like brain damage without driving resistance in *P. gingivalis*, and in a small trial in humans it improved inflammation and some measures of cognition. A large trial is now under way.

But as all these diseases involve inflammation, why not just block that? If we did, it could leave you open to the germs that this immune response does fight off or block other vital things that immune signals do. That's why some companies are working on drugs to block only specific inflammatory signals. But tampering with our complex immune systems without doing damage – as *P. gingivalis* shows – will be a significant challenge.

(see diagram, page 45). If this goes on too long, an oxygen-poor pocket develops between gum and tooth. A handful of bacteria take advantage of this and multiply. One of them, *Porphyromonas gingivalis*, is especially insidious, disrupting the stable bacterial community and prolonging inflammation.

This might seem a strange thing to do. Most pathogens try to block or avoid inflammation, which normally kills them before it shuts down again. Starting in our 30s and 40s, this shutdown begins failing, leading to the chronic inflammation involved in diseases of ageing. No one knows why.

P. gingivalis may have a hand in it. It actually perpetuates inflammation by producing molecules that block some inflammatory processes, but not all of them, says Caroline Genco of Tufts University in Massachusetts. The resulting weakened inflammation never quite destroys the bacteria, but keeps trying, killing your own cells in the process. The debris is a feast for *P. gingivalis*, which, unlike most bacteria, needs to eat protein.

The destruction also liberates the iron that bacteria need and which the body therefore normally keeps locked up. "These bacteria manipulate their interaction with the host immune response to enhance their own survival," says George Hajishengallis at the University of Pennsylvania.

Gum control

Eventually, the infected tooth falls out – but long before that *P. gingivalis* escapes into the bloodstream. There your immune system makes antibodies against it, which usually defend us from germs. But *P. gingivalis* antibodies seem to be more a mark of its passing than protection. People with these antibodies are actually more likely to die in the next decade than those with none, and more likely to get rheumatoid arthritis or have a heart attack or stroke.

This could be because, once in the blood, *P. gingivalis* changes its surface proteins so it can hide inside white blood cells of the immune system, says Genco. It also enters cells lining arteries. It remains dormant in these locations, occasionally waking to invade a new cell, but otherwise remaining hidden from antibiotics and immune defences. However, even hunkered down within our cells, *P. gingivalis* continues to activate or block different immune signals, even changing a blood cell's gene expression to make it migrate to other sites of inflammation, where the bacteria can hop out and feast again.

"A bacterial cause could explain the genetic risk for Alzheimer's"

One explanation for why gum disease makes you more likely to get conditions like diabetes and Alzheimer's disease is that it adds to your general "inflammatory load". But *P. gingivalis* may act more directly too: the bacteria have been detected in inflamed tissue in the brain, aorta, heart, liver, spleen, kidneys, joints and pancreas in mice and, in many cases, humans.

The strongest case against *P. gingivalis* is as a cause of Alzheimer's disease. This constitutes more than two-thirds of all dementia, now the fifth largest cause of death worldwide. It was long blamed on the build-up of two brain proteins, amyloid and tau. But that hypothesis is crumbling: people with dementia may lack this build-up, while people with lots of the proteins may have no dementia – and most damningly, no treatments reducing either have improved symptoms.

Then, in January, teams at eight universities and the San Francisco company Cortexyme found a protein-digesting enzyme called gingipain, produced only by *P. gingivalis*, in 99 per cent of brain samples from people who died with Alzheimer's, at levels corresponding to the severity of the condition. They also found the bacteria in spinal fluid. Giving mice the bacteria caused symptoms of Alzheimer's, and blocking gingipains reversed the damage.

Moreover, half of the brain samples from people without Alzheimer's also had gingipain and amyloid, but at lower levels. That is as you would expect if *P. gingivalis* causes Alzheimer's, because damage can accumulate for 20 years before symptoms start. People who develop symptoms may be those who accumulate enough gingipain damage during their

Linking dementia and gum disease
Hear Sim Singrao discuss oral health and Alzheimer's risk
newscientistlive.com/gum-disease

lifetimes, says Casey Lynch at Cortexyme.

Still, dementia researchers have questioned how a bacterial cause can account for genetic risk factors for Alzheimer's. But it may actually explain them, according to a team in Sweden. The people with the highest genetic risk produce a particular form of an immune protein called ApoE that is destroyed in the disease. Last year, Swedish researchers discovered that gingipains are better at destroying that particular ApoE than other forms.

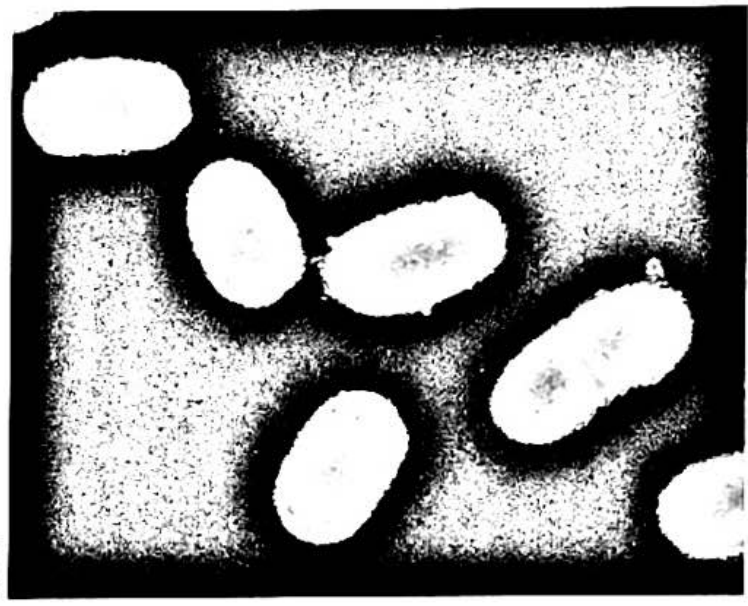
P. gingivalis may literally break our hearts too. There is growing evidence for a causal link to atherosclerosis, or "hardening of the arteries". Researchers have found *P. gingivalis* in the fatty deposits that line arterial walls and cause blood clots. When bits of clots clog blood vessels in hearts or brains, they cause heart attack and stroke.

The bacteria trigger the molecular changes in artery linings that are typical of atherosclerosis, says Genco. We have also found that *P. gingivalis* creates the lipoproteins thought to trigger atherosclerosis, causes it in pigs and affects arteries much like high fat diets. Lakshmyya Kesavalu at the University of Florida, who has cultured viable *P. gingivalis* from the atherosclerotic aortas of mice, calls the bacteria "causal".

The American Heart Association agrees that gum disease is an "independent" risk factor for cardiovascular disease, but doesn't call it causal. It argues that although treating gum disease improves hardened arteries, no studies have found that it reduces heart attacks or strokes. But, according to Steve Dominy at Cortexyme, that could be because, while gum treatment helps arteries by easing inflammatory load, it doesn't eradicate the *P. gingivalis* already in the blood vessels. Clinical trials are needed to firm up the connection, but these are expensive and difficult – especially when the bacterial hypothesis is still in its early days.

The link is clearer for type 2 diabetes, in which people lose sensitivity to insulin and eventually can't make enough to control blood sugar. It is currently a pandemic, blamed on the usual lifestyle suspects.

***Porphyromomas gingivalis* evades our defences and drives inflammation**



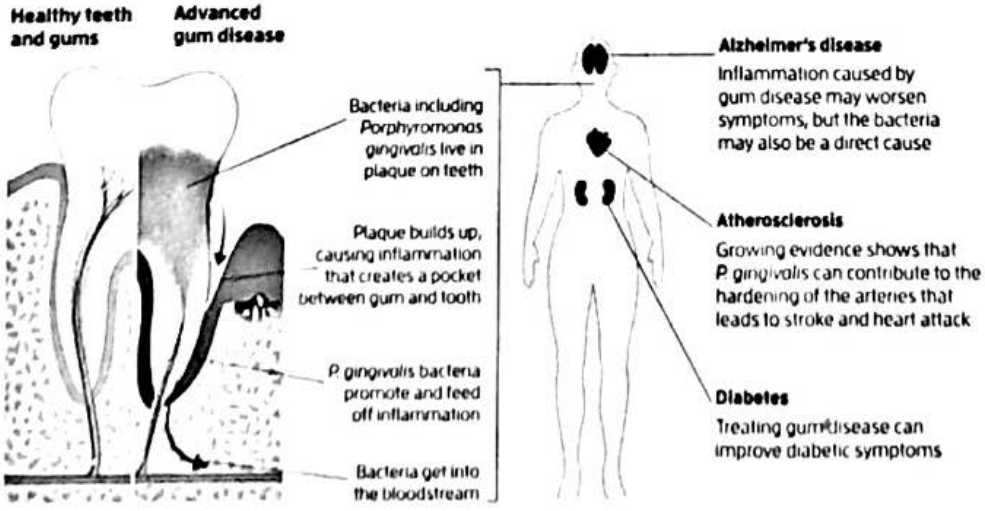
Diabetes worsens gum disease, because high blood sugar levels hurt immune cells. But gum disease also worsens diabetes, and treating it helps as much as adding a second drug to the regimen taken by someone with the condition, according to the American Academy of Periodontology. Treatment is now recommended by diabetes associations, yet none of them list gum disease as a risk factor. As with other conditions, there is evidence that *P. gingivalis* isn't promoting diabetes just by adding to the body's inflammatory load, but may also be acting directly in the liver and pancreas to cut insulin sensitivity.

"It is very hard to prove causation in a complex disease," says Genco. We know that mice given a mouthful of *P. gingivalis* get gum disease – and diabetes, rheumatoid arthritis, atherosclerosis, fatty liver disease and Alzheimer's-like symptoms. We know that, in humans, gum disease makes the other diseases more likely, and that *P. gingivalis* lurks in the affected tissues and makes the precise cellular changes typical of these conditions.

If these diseases actually share a more direct cause, it might finally suggest cures (see "Master of concealment", far left) – as well as explaining just how the same bad habits bring them all on. People who drink more alcohol tend to have more *P. gingivalis* and are more susceptible to gum disease. Tobacco smoke helps the bacteria to invade gum cells. Exercise, the only known way to lower your risk of Alzheimer's, improves gum disease by damping inflammation and ending *P. gingivalis*'s feast. ›

Down in the mouth

A new hypothesis suggests that the bacteria behind gum disease may also cause many more serious conditions



Germ theory

A range of bacteria may play a role in supposedly non-communicable diseases. *Propionibacterium acnes*, for instance, is best known for causing acne, but also seems to damage the discs that cushion your spinal vertebrae, a common cause of severe back pain, says Ondrej Slabý of Masaryk University in the Czech Republic. It has also been implicated in prostate cancer. But it is *Porphyromonas gingivalis* that has been linked to the widest array of conditions:

RHEUMATOID ARTHRITIS

P. gingivalis is present in the joints of people who get this condition before symptoms appear and is the only bacterium known to make a chemical involved in the disease.

PARKINSON'S DISEASE

P. gingivalis and its protein-munching enzymes, gingipains, are found in the blood of people with Parkinson's disease, and promote the inflammation and abnormal clotting seen in the condition.

KIDNEY DISEASE

Gum disease is associated with chronic kidney disease and gum treatment seems to help the kidneys.

FATTY LIVER DISEASE

There is far more *P. gingivalis* in affected livers than in healthy ones, and it worsens the disease in mice. Treating the gums helps.

CANCER

The bacteria has been found in early-stage cancers of the mouth, oesophagus, stomach and pancreas, and changes cell functions in ways typical of these cancers.

MACULAR DEGENERATION

Injecting the bacteria into the retina seems to damage eyesight by producing age-related macular degeneration in mouse studies.

PRETERM BIRTH

Gum disease, caused by *P. gingivalis*, has been established as a risk for premature birth.

If gum disease bacteria drive many other conditions, we could stop them early

"It's too easy to mock the notion that flossing may contribute to brain health"

Then there is diet. Douglas Kell at the University of Manchester, UK, believes our blood contains many dormant bacteria, needing only a dose of free iron to awaken and cause disease. That could be why eating too much red meat and sugar or too little fruit and veg lead to these diseases: all increase your blood iron.

The long haul

No official medical advice for warding off these diseases includes "see your dentist", at least not yet. "Periodontal disease should be better recognised by the community as a clearly established risk factor," says Dominy. One of the clearest risks is for Alzheimer's. But guidelines for avoiding Alzheimer's published in May by the World Health Organization (WHO) say nothing about preventing gum disease.

"There is insufficient evidence to suggest that treating gum disease reduces the risk of dementia," says Benoit Varenne at the WHO, echoing the verdict on heart disease, even though the same caveats probably apply. The guidelines recommend avoiding diabetes and high blood pressure, despite stating that there is little or no evidence that this stops Alzheimer's.

"It's perhaps too easy to mock the notion that flossing your teeth may contribute to good brain health," says Margaret Gatz at the University of Southern California. And that may be part of why this idea hasn't yet taken off in mainstream medicine. "There is a history of dental and medical doctors working apart and not cooperating," says Thomas Kocher at the University of Greifswald, Germany.

But it also reflects the long-held belief that heart attacks and the other conditions are primarily the result of bad lifestyle, not bacteria. Such underlying paradigms in science can take decades to change. That happened when bacteria, not stress and stomach acid, were shown to cause stomach ulcers. After decades pursuing these explanations, many medical experts are reluctant to admit that amyloid may not cause Alzheimer's and high cholesterol may not lead to heart disease.

With the world's population ageing, we don't have decades before these diseases become a health crisis severe enough to break health systems and societies. We need a new paradigm. That means facing the possibility that it may all be down to germs, after all. ▮

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