

A White Paper

It's Time to Find the “Alzheimer's Germ”

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Alzheimer's disease, the sixth-biggest cause of death in the U.S., continues to increase alarmingly, with 303 dying per day. Despite billions of dollars spent on research over decades, its root cause is still unknown. So far, there is no simple diagnostic test, cure, or preventive.

Most research efforts, and monies, so far have been focused on two suspicious items found in patients' brains, amyloid plaques and protein tangles. However, few clinically helpful results have yet been obtained.

An intense review of the scientific literature revealed that many aspects of Alzheimer's disease resemble patterns of infections seen with known bacteria, viruses, fungi or prions. These include presence of microbes within the brain, inflammation, and positive effects of antibiotics. Also, transmission of Alzheimer's may occur within households and in the neurosurgical operating room. But these and other intriguing leads have never been followed up in depth.

So far, with minor exceptions, neither scientists nor government agencies expert in known infectious diseases and epidemics have been significantly involved in Alzheimer's research.

In 2016, 33 prominent Alzheimer's researchers signed an editorial pleading for increased funding and priority for further investigations of an infectious cause of the disease. However, despite huge sums being appropriated for research, there has been little realignment of grant priorities to date, and current amounts devoted to possible infectious causes of Alzheimer's are paltry.

Dr. Leslie Norins asserts that there is just one germ, known or yet to be discovered, that is the root cause of Alzheimer's. He urges the major funders of research to promptly increase or re-prioritize their grant allotments to thoroughly search for this

To jump-start the necessary studies, Alzheimer's Germ Quest, Inc, is offering a \$1 million challenge award for the scientist who—before 2021—provides persuasive proof of the identity and role of the theorized germ. (ALZgerm.org).

It's Time to Find the "Alzheimer's Germ"

By LESLIE C. NORINS, MD, PhD, F(Em.)IDSA

If a mystery disease is killing 303 people per day, and there's a chance it's caused by an infection, aren't all government germ detectives and labs in full investigative mode, 24/7? Of course—unless it's Alzheimer's disease (AD). Which it is.

U.S. deaths in 2015 (most recent year available) were 110,561. That's 303 dying per day. It's now the fifth leading cause of death. Cases are up 89 percent since 2000, says the Alzheimer's Association. There's no cure or preventive. And Congress says care of Alzheimer's patients costs \$153 billion a year.

If these numbers were instead newborns with microcephaly (Zika), deadly pneumonias (Legionnaire's disease), or deadly cancers and wasting (AIDS), a public health emergency would have been declared, and there would be a crash program in progress right now to search for a possible infectious cause. That turned out to be the answer with these other initially mysterious afflictions.

From a two-year review of the scientific literature, I believe it's now clear that just one germ—identity not yet specified, and possibly not yet discovered—is the root cause of most AD. I'm calling it the "Alzheimer's Germ" (AG). I purposely use the umbrella term "germ", so as to not exclude any possibility, such as bacterium, virus, fungus, parasite, prion, or something new.

Why hasn't this suspected germ already been found, and indicted, with persuasive proof of its damaging role as the root cause of AD? Three reasons: (1) Too few researchers have been looking in the right places. (2) Only a few of the many classic and newer techniques for germ and immune response detection have so far been brought to bear. (3) There has so far been little collaboration between experts in Alzheimer's research and those investigating traditional and unusual infectious diseases.

I wish the whole explanation were merely a shortage of money. But several billion research dollars (that's a "b"), and decades, have been spent on exploring two peculiar substances found in the brains of living and dead AD patients, amyloid plaques and protein tangles. Initially it seemed logical to do this. But clinically useful results so far? Little or none, except for help in diagnostic imaging.

So, it's time to move Alzheimer's from its perennial status of "research project" to the highest priority of emergency microbiological search. Finding an infectious cause will open pathways to effective diagnosis, treatments, and prevention.

For convenience, with a few exceptions references are not inserted for medical facts presented in the text which follows. However, all were obtained directly from scientific papers in research journals or similar credible sources.

Ten intriguing clues the Alzheimer's germ exists

1. The normal human brain is not sterile, but contains many bacteria, particularly Proteobacteria and Actinobacteria. Spirochetes and oral bacteria have also been repeatedly identified, as have viruses, including herpesvirus.
2. It is not unusual for pathogenic organisms to invade the central nervous system.
Examples of this include:
 - Bacteria: Neurosyphilis, leprosy, meningococcal meningitis. chlamydia
 - Viruses: Zika, measles, chickenpox, Epstein-Barr virus, West Nile, HIV, polio, cytomegalovirus. Recently, herpes 6A and 7 were spotlighted as excessively present in AD brains. (Neuron. 2018 Jul 11;99(1):64-82.e7. doi: 10.1016/j.neuron.2018.05.023. Epub 2018 Jun 21.)
 - Parasites: Malaria, toxoplasma, amoeba
 - Prions: Kuru, Creutzfeldt-Jakob disease, "Mad Cow" disease.
3. Bacteria can produce substances which damage the nervous system. C. tetani spores manufacture a toxin which harms motor neurons (lockjaw). The toxin made by spores of C. botulinum blocks nerve transmission, causing paralysis (botulism).
4. Amyloid beta, a prominent protein accumulating in the AD brain, can be incited by various microorganisms. A recent paper describes its production being stimulated by herpes virus, and suggests it plays a protective role. (Neuron. 2018 Jul 11;99(1):56-63.e3. doi: 10.1016/j.neuron.2018.06.030.)
5. Inflammation, an emerging topic in AD research as a proximate cause of neuronal damage, is not a root cause, but a result of some invasion or injury. Bacteria, viruses, fungi, parasites and prions can trigger it.
6. A serious disease in older adults may be caused by virus from a childhood infection which has remained hidden in the patients' nerves for decades, only to

surface as they age, e.g. chickenpox virus (herpes zoster) later erupting as shingles. Some adult infections, e.g. syphilis, can take decades to transit from initial minor or unnoticed infection to brain damage. Kuru has been reported to have an incubation period of up to 50 years. Chlamydia and toxoplasma have been reported to remain quiescent in the body for decades. So, AD developing in seniors may be the delayed manifestation of an infection much earlier in life.

7. Various drugs known to ameliorate or cure infections have been reported to have a beneficial effect on Alzheimer's patients. Certain antibiotics which kill bacteria seem to improve AD patients (J Am Geriatr Soc. 2004 Mar;52(3):381-7) and amyloid plaques (Scientific Reports 6:30028. DOI:10.1038/srep30028.) Anti-herpetic therapy administered to a large group of Taiwanese seemed to decrease the subsequent incidence of AD, and patients who had untreated herpes infection earlier in life developed AD at a greater rate than non-infected people. (Neurotherapeutics. 2018 Apr;15(2):417-429. doi: 10.1007/s13311-018-0611-x)
8. AD may be transmissible in some households. The Cache County study reported caregivers whose spouses had dementia had greater risk of dementia themselves than did caregivers whose spouses did not have dementia. (J Am Geriatr Soc. 2010 May;58(5):895-900. DOI: 10.1111/j.1532-5415.2010.02806.x.). The authors attributed the caregivers' Alzheimer's to a proclivity caused by the stress of caring for patients with the disease. The study was not designed to detect possible transmission, and data are not complete enough to be conclusive. The authors do not comment upon this possibility.
9. AD may be transmissible in the neurosurgical operating room. Neurosurgeons, who of course operate on brains, were reported to die from Alzheimer's at an unusually high rate compared to other causes. (J. Neurosurg 113:474-478, 2010. DOI:10.3171/2010.1.JNS091740.) This compilation was not designed to illuminate this intriguing, unexpected finding, and the authors do not comment upon it. The data are insufficient to be determinative. Transmittal of amyloid beta was reported to result from dura mater grafts and from neurosurgical procedures. (Jaunmuktane Z et al, Acta Neuropath 135:671-679, 2018. DOI.org/10.1007/s00401-018-1822-2.)

10. AD may be transmissible to non-human primates, with difficulty. Investigators who had successfully established kuru as a transmissible disease injected AD brain material into several species of non-human primates. After prolonged observation periods, usually over 40 months, of 61 inocula from 19 AD brains, three produced spongiform encephalopathy in the animal recipients. The investigators state this rate of apparent transmission is much less consistent than they found with material from kuru and Creutzfeldt-Jakob disease, and discuss other uncertainties. A later re-examination of the original tissue blocks reports transfer was more successful than initially thought. (Goudsmit J et al. *Neurology* 30:945-950. 1980; Goldgaber D et al, *Alzheimer's & Dementia* 2010 6:S250 DOI: <https://doi.org/10.1016/j.jalz.2010.05.815>).

Little research hunts the “Alzheimer’s germ”

Huge sums of money are being poured into Alzheimer’s research grants. The NIH alone lists its expenditures for 2018 as about \$2.3 billion. Additional financial support is provided by governments, advocacy organizations, and foundations around the world. Bill Gates is disbursing \$50 million for AD research, and another \$50 million for related venture investments. Other philanthropists are also contributing.

Of this torrent of research money, how much is going toward searching for a germ, possibly yet undiscovered, as the cause of Alzheimer’s? The brutal answer is “only a few dollars”. (I recognize this frank assessment may evoke rejoinders from some funders and researchers that a few existing or contemplated projects will, or might, relate to this possibility. But even so, current research grants in this direction are paltry compared to other funded aspects).

To quantify this situation, I conducted a search of a master compilation of Alzheimer’s research topics, known as CADRO (Common Alzheimer Disease Research Ontology), which was prepared collaboratively between NIH’s National Institute on Aging and the Alzheimer’s Association. Category A, the first section, is “pathogenesis,” i.e. causation. It provides 12 categories, which are subdivided into a total of 59 research topics, into which scientists can classify their project. There is no classification mentioning any possibly causative “germ” invaders such as bacteria, viruses, fungi, parasites, or prions.

In July 2017, the Alzheimer’s Association convened an international conference in London at which researchers “from 70 countries” could share progress. The program reflected the current research areas receiving most emphasis worldwide. The keyword index of the numerous presentations showed, not surprisingly, the largest number of entries (110) for amyloid/APP. The next most common item was tau, the tangled protein, with 85 entries. Inflammation—the body’s reaction to something—had 45 mentions.

In contrast, presentations of definite germ importance had only single digit presence: prion proteins (8 entries), infectious disease (4 entries), bacteria (1 entry). Virus was not even listed as a keyword.

No Alzheimer's research interest group on "germs"

One of the most prominent associations of researchers interested in Alzheimer's is the International Society for Advancing Alzheimer's Research and Treatment, commonly known as ISTAART. (Disclosure: I am a recent member). I viewed its online membership information as a reasonable representation of current research interests.

ISTAART currently has about 2400 members. Those interested in a particular subject can create a PIA (Professional Interest Area). Currently there are 18 such groups.

There is no group listed for an extrinsic cause of AD, or an even narrower one interested in finding a causal bacterium, virus, prion or other infectious agent.

Infectious disease epidemiologists have never investigated leads

When cases of a disease seem to occur at a greater frequency in certain settings, public health and medical epidemiologists often leap to attention, and intensely investigate to determine if a responsible factor can be pinpointed. Thus, the causes of many initially mysterious afflictions have been determined. Example: puzzling microcephaly in infants was traced to Zika infection of the mothers—who sometimes had no symptoms.

Consider clues 8 and 9 (above). The appearance of AD was increased abnormally in two settings: individuals caring for somebody with AD and neurosurgeons' cause of death. To anyone with an infectious disease background and a detective's inclination, these two findings would immediately raise the possibility—but of course not prove—a "transmissible agent" is at work.

Puzzling findings in caregivers of Alzheimer's patients

Why would caregivers of Alzheimer's patients apparently have more AD than caregivers of other types of patients? The original researchers attributed it to the great stress of this particular niche of caregiving. Maybe. But it also fits with transmission of an infectious agent from the patient to the caregiver.

After all, caregivers are in close proximity to the AD patient for hours. There is sneezing, coughing, feeding, bathing, and toileting. Plus household members share many dishes, cloths, furniture, etc. Plenty of opportunities for a germ to spread.

Another study found that blood markers of inflammation (C-reactive protein and tumor necrosis factor- α) were higher in caregivers of AD patients than in controls. Also, after the spouse receiving the care died, the caregiver's inflammatory blood markers declined, including a lesser-known one, sICAM-1

(soluble intercellular adhesion molecule). [von Kanel, R et al, *Gerontology*. 2012; 58: 354–365. doi:10.1159/000334219]. Again, the investigators attributed the rise and later drop in blood markers of inflammation to the stress of caregiving, which was terminated by death of the patient.

But a similar pattern of change in inflammatory markers can be caused by presence of an infectious challenge, which is then removed. This possibility was never considered by the researchers. However, I don't fault them; remember it is not yet "acceptable" to many Alzheimer's researchers and funders that infection at least needs investigating.

Could Alzheimer's be a neurosurgical hazard?

Why would Alzheimer's be a leading cause of death for neurosurgeons (Clue 9)? Here's the theoretical, not-yet-investigated reason. These highly skilled professionals are constantly exposed in the operating room to living brain tissue of patients, some of whom are destined to develop AD—and a few who may already have AD's earliest stage, mild cognitive impairment. The surgeons do wear rubber gloves, but puncture wounds from instruments and sharp fragments of skull bone nevertheless occur. That is why HIV and hepatitis infections are recognized as transmissible hazards for surgeons. But Alzheimer's has never been similarly investigated.

The above scenarios are quite compatible with spread of a germ. However, of course, a careful investigation would have to rule out other possible causes, and even statistical flukes. But here's the point: no epidemiologists experienced with infectious diseases have yet undertaken the necessary deeper studies.

Infections emphasis rises in 2016

In April 2016, a group of 33 prominent Alzheimer's researchers authored an editorial in *Journal of Alzheimer's Disease* urging more research on infection as a possible cause of AD. They noted several known agents that seemed relevant: herpes simplex virus, spirochetes, chlamydia, HIV, parasites, fungi, and prions.

However, their plea has not yet been reflected in any major shifts in research funding. The "big two" grant money targets are still the supposed villains, amyloid plaques and tau protein tangles. However, no clinically useful treatments have been obtained from research on them.

Also in 2016, a research team at Harvard postulated that the beta-amyloid plaques characteristic of Alzheimer's pathology are a kind of immune response to invasion, perhaps repeated ones, by already-known germs or other factors. Other scientists have flagged herpes, spirochetes, chlamydia, toxoplasma, and fungi as possible triggers.

And in 2017, a new book appeared for professionals: *Handbook of Infection and Alzheimer's Disease*, Editor J. Miklossy, IOS Press. Amsterdam. ISBN 978-1-61499-705-4. This volume provides a much-needed assemblage of information on microbial aspects of AD. Caution: not all researchers agree with each and every assertion by each scientist, or the research behind it. But all the chapter authors

believe that infectious processes of one sort or another are root causes of AD. The volume is valuable even as a compendium of references.

Thus, after many years of “infections” being dismissed out of hand and largely ignored by funders, the research climate for investigating them may be getting better. The relatively few infection theorists to date have cited organisms already recognized. Maybe those are culprits, maybe not. (The real villain might be a currently unappreciated organism waiting to be spotlighted or even discovered). But at least these openly expressed, once-heretical views now make it more respectable to search for an AG.

Recent: inflammation, microbiome, gut-brain axis, and phages

Despite the reticence of research funders to prioritize grant applications outwardly labelled as illuminating the role of germs, some pertinent studies were sufficiently camouflaged, probably innocently, to get funding anyway. Some of these apparently acceptable disguises which can obviously include work on “germs,” have been inflammation, microbiome, gut-brain axis, and phages.

But should “inflammation” be counted as tiptoeing up to “germs”? Yes, and here’s why. Inflammation is a process, not a cause. It is the body’s reaction to something. Many germs can incite it, but it can also arise from trauma, toxic chemicals, the body’s own immune system mistakenly attacking the body, etc. Thus, to state that AD is “caused by” inflammation is not a final answer; we must demand to know what triggered the inflammation in the first place—and if germs are playing that role.

Inflammations resulting from infections by various known pathogens were also posited to cause leaky blood vessels, thus allowing intravascular substances to leak out and damage nerve cells in the brain.

The microbiomes of the brains and guts of Alzheimer’s patients are now receiving increasing attention. Differences have been found between AD cases and controls. The significance of these is not yet clear.

In Parkinson’s disease, another neurodegenerative illness, researchers reported the populations of intestinal phages differed markedly in patients versus controls. The researchers speculated that bacterial fermentation products which affect folding of crucial proteins could travel up the vagus nerve (gut-brain axis) to cause damages in the brain.

Why hasn’t the Alzheimer’s germ been found in 110 years?

Short answer: Suspect germs have been spotlighted by a number of scientists, but persuasive proof they cause AD is still lacking. Perhaps these microbes were only innocent bystanders, or facilitators, or they entered the picture after initial damage was done by some other invader or process. More research is urgently needed to sort this out. Serological tests of blood samples collected over time may help pinpoint the rise of antibodies, antigens, or nucleic acids of the villainous agent.

Moreover, it can take decades, or centuries, to acquire new research findings to overturn fervently held—but wrong—beliefs as to the cause of an illness.

Alois Alzheimer published the account of his first patient in 1907. By then, a few diseases had been proven to be caused by bacteria, e.g. anthrax, tuberculosis and cholera. In the years that followed, numerous other afflictions supposedly due to other factors were determined to be infectious in origin.

For example, malaria had been attributed to harmful “miasma” vapors from swamps (cause found to be a parasite), and polio to filth (cause found to be a virus).

Even in recent decades, an infectious cause has been slow to be identified for various diseases. The Legionnaire’s disease bacterium was not identified until the year following the 1976 epidemic which named the disease. Then, retrospective studies of frozen specimens revealed it was also the culprit in unsolved “mystery” epidemics which had occurred in earlier years.

Kuru, a mysterious, supposedly hereditary affliction of the nervous system, was investigated in 1957, but only in 1966 was it proven to come from a transmissible agent which couldn’t be cultured or seen microscopically, and which was spread by eating the brains of deceased relatives.

A germ was belatedly discovered—after years of skepticism and even ridicule—to be causative in other diseases previously not considered to be infectious, e.g. cervical cancer (human papilloma virus) and gastric ulcer (*H. pylori*).

More recently, reflect on the headlines about SARS, Zika, HIV/AIDS, “flesh-eating bacteria,” Ebola, and other infections, to realize not all disease-causing germs had been recognized by the time you were born. Therefore, it is logical to expect discoveries of such previously unappreciated agents to continue.

Thus, the fact that no germ has yet been indicted as the trigger for a disease of unknown cause, like AD, in no way excludes one being pinpointed in coming years.

The Alzheimer germ may already be appearing in labs

There’s a slim chance the AG could be “hiding in plain sight”. By this I mean it might readily grow on one or more of the nutrient concoctions used routinely to grow bacteria or viruses in the lab.

So, when blood, sputum, or spinal fluid from an Alzheimer’s patient who happens to become acutely ill and feverish is being tested for the presence of a typical infection, such as pneumonia, the AG may also be present in the sample and grow along with whatever other microbes are there.

However, because nobody is looking for any germ other than one to blame for the obvious infection, the AG growing will be called a “contaminant,” and disregarded.

The Alzheimer's germ might need special conditions to grow

But maybe the AG will have special nutritional requirements in order to grow in the lab—assuming it can indeed be grown outside the body. Nobody knows in advance what these will be. Some germs are picky eaters. Therefore, patient samples that might contain the AG will have to be placed onto, or into, each of the wide array of lab “foods” available, hoping that at least one of them will encourage it to multiply so it becomes more apparent. Eggs and tissue cultures of various cells may also have to be inoculated in case the AG is a type of virus or rickettsia.

The right nutrients can be crucial. For example, the Legionnaires bacterium grew on only one of 17 common bacterial media (lab food blends) tested. It was initially found only because Dr. Joseph McDade, at CDC, had inoculated patient samples into eggs, looking for rickettsia; luckily, the Legionnaires bacteria also grew there. And fortuitously his dedication brought him back to his lab during the Christmas holidays to further examine samples microscopically—and he noticed it.

The right lab conditions play a role too. The Legionnaire's bacterium needs an atmosphere with augmented carbon dioxide. So does the gonococcus—which can be asymptotically infecting women. Without the extra CO₂ there's little growth.

And patience may be necessary. While bacteria like staph and strep multiply quickly enough to be visible in a day or two, mycobacteria (TB) can take weeks. The pinpointing of *H. pylori* as the cause of gastric ulcers was delayed because culture samples were—by protocol for other infections—discarded by the lab after two days. It turned out that this new bacterium required several extra days to grow sufficiently to be noticed.

Routine clinical labs might fail to grow it

Most all clinical labs in the U.S. are highly competent. There are periodic distributions of test samples to tests to confirm their proficiency with likely organisms. However, newer infectious organisms may prove a challenge. For example, the College of American Pathologists was said to find that “as many as two-thirds of clinical microbiology laboratories were unable to grow a pure and heavy culture” of the Legionnaire's bacteria. Thus, it might take a highly experienced lab focusing on finding the AG to detect it.

But clinical microbiology labs are under pressure to detect known germs in samples from sick patients; there's no time or inclination to search for, or identify, an as-yet-undiscovered microbe.

Will the Alzheimer's germ produce effects in research animals?

Mice and rats. These are the laboratory animals most often inoculated in research on germs that cause human disease. But what happens? Sometimes the bacteria or virus will indicate its presence by killing the animal. Other times it may cause only visible signs, like accumulation of fluid in the

abdomen. Or there may be no apparent effect, even if the germ can be found to have distributed itself, silently, throughout the animal's body.

Animal species might be crucial

Which species of lab animal would be optimal to inoculate with the possible AG? It's hard to guess in advance. If one goes by popularity, which includes cost and convenience, here are percentages of species used in research, as compiled by the European Union: Mice 59, rats 18, fish 9, birds 6, rabbits 3, other rodents 2, and reptiles 1.

A National Library of Medicine compilation from published research found 50,000 studies used mice and 36,000 employed rats. Just 1300 used guinea pigs (despite the appropriation of that name to indicate human research subjects).

Thus, you can see that mice are the candidates in first place. They are already heavily used in research on various non-infectious facets of AD, but nobody yet knows if they would be the best species to reveal an AG.

A number of germs take hold only in less common—and less convenient—animal hosts. Consider ferrets.

They're tricky to handle; they also bite vigorously. They are great for influenza virus research (but measles virus won't take hold in them.) Some can be infected with the agent of SARS (severe acute respiratory syndrome), but they resist MERS (Middle East respiratory syndrome).

Leprosy bacillus? The armadillo is the go-to. Syphilis bacteria most conveniently grow in the rabbit. Is anybody injecting Alzheimer's materials into such species? No.

Bottom line: few if any species of laboratory animals have been yet examined for susceptibility to the AG, and finding the right one could be critical. But even proving the possible agent took hold or multiplied in the injected animal could be difficult, as in advance one might not know what signs to look for.

Non-human primates a challenge

It's logical to think of studying chimpanzees and monkeys, as they are similar to humans in so many ways. But this could be difficult, given today's tensions about research using animals, especially ones that are cousins to humans. Recently, chimps in the U.S. have been officially "retired" from research, and they are considered an "endangered species."

However, chimpanzees were essential to show kuru was caused by a transmissible agent (but it took a couple of years before the inoculated animal began to show the characteristic paralysis).

Macaques, a monkey-like primate, were important for progress on HIV and Ebola.

I was intrigued by a recent report that Alzheimer-like plaques were found in brains of chimpanzees. I recalled that HIV and other viruses are theorized to have crossed over into humans from forest primates, so maybe this discovery indicated that an animal form of the AG was present in chimps, and in the past had crossed over to humans.

Or, perhaps samples of blood or tissue from AD patients could transmit the disease to chimps, which have so many biological similarities to us. However, there is considerable opposition to any further medical research using this species. Administrators open to all possibilities of an Alzheimer's cause should already be convening panels to chart an acceptable ethical path.

What would Alzheimer's look like in a lab animal?

How would you recognize AD in animals? Amyloid plaques in the brain could be exciting, but they don't guarantee dementias even in humans. Protein tangles? Still being defined. Deterioration of cognition? It's hard to assess the mental processes of lab animals, let alone prove they are identical to people's. In desperation, some AD scientists have trained mice and rats to navigate mazes, and studied deterioration in this ability.

Brain samples have gotten the spotlight

Because deterioration of cognition clinically, plus visible brain plaques at imaging and at autopsy, are hallmarks of AD, it seemed logical to early scientists to assume that AD's cause would be found in brain specimens. That's the reason generous donors have provided brains post-mortem to the several brain banks that exist.

The formalin-preserved bits of brain tissue are perfect for the study of tissue architecture. Perhaps some dead, preserved AGs are still within these specimens, and can be visualized if the many chemical stains for microorganisms are each tested.

The fresh-frozen samples are currently used in a variety of biochemical and genome studies. Maybe the AG, in suspended animation, is within these, and can be coaxed to grow if the right nutrients can be found for it. Certainly, it would be worth trying an array of microbiological foods. Also, PCR and related techniques can reveal nucleic acids indicating that bacteria and viruses were there.

But nobody knows if the AG, dead or alive, is in the brain samples. Perhaps the patient's body disintegrated the germ, or cleared it away, before fatal damage set in.

Final hurdle: if bacteria are visualized in the brain samples, or even grown, were they causing the AD or were they just innocent bystanders who happened to be in the neighborhood? Further studies, such as testing of serum samples for antibodies or germ components, will be needed.

Necessity to search the entire body

Lab animal studies of the new AG might reveal it spreads silently, early on, throughout the animal's body, like in syphilis and tuberculosis. But later, it only "acts up" preferentially in certain organs—like the brain. In a different species, it's not even guaranteed that it will attack the animal's brain; maybe it will select the spinal cord, or even the kidney, or lung.

So, the singular focus on "brain", though understandable and logical in the beginning, is no longer enough. The search for the AG must be expanded to all organs, tissues, and bodily fluids.

Serum samples must be tested in addition

Infectious disease detectives have broader needs than samples of the organ that appears to be the focus of an infection. They want samples of blood serum from the patients. A simple venipuncture can obtain the necessary blood. In the usual epidemic, this consists of a specimen at the time of observable disease, and a sample after the patient recovers. A treasured addition, though in the usual situation unobtainable, is serum from before the patient became ill at all.

These two or three samples enable the scientists to work out if the germ being studied has triggered a specific immune response by the body. Or, whole organisms or fragments might be detectable. If so, marked changes in levels of these over time render the organism a prime suspect.

The most valuable collecting of serum samples, going on in several countries and projects, is obtaining periodic specimens from volunteers who are being followed as they age, i.e. longitudinal samples. Some of these people will develop AD. Then, researchers can look back at the specimens collected over the years from these individuals and assess what factors have changed—especially which occurred early, before dementia showed itself. Identifying these might provide a blood or urine test to warn of future AD—and thus allow intervention.

How can serum samples be obtained?

I inquired of a British brain bank administrator whether brain banks there collect and save serum samples from AD patients, either serially during life, or at post-mortem examination. He said they do not.

In the U.S., NIH's National Institute on Aging funds regional centers to collect brain specimens from patients dying of AD and other neurodegenerative diseases. Many times, single serum samples are also obtained at death, or during drug trials. These can be requested by researchers.

In a few research centers, serum samples are obtained over time from living patients and normal volunteers as they age. Other sequential samples are obtained from AD patients being monitored as part of drug trials. Testing these "longitudinal" collections from individuals will enable researchers to ascertain if and when there has been an immune response to the AG.

Biggest serum bank not yet tapped for Alzheimer's research

The world's largest serum bank contains 55 million specimens from 10 million individuals. The first samples were collected 28 years ago, but the collection grew considerably in recent decades. Apparently, it hasn't yet been used to any extent for Alzheimer's research. It's the U.S. Department of Defense Serum Repository, commonly abbreviated as DoDSR.

Never heard of it? Don't feel bad; most researchers don't know this valuable resource exists, though it's never been classified as secret.

The DoDSR contains large numbers of samples from active military personnel and veterans. Even some from military families and a few civilians. In many instances, the same individual gave samples over time.

One of the main "mental" research interests of the military is post-traumatic stress disorder, better known as PTSD. Another is TBI (traumatic brain injury). However, the repository's holdings are cooperatively available for most any worthwhile project. Without doubt, the growing burden of AD is of great concern to military medicine officials and the Veterans Administration.

As military staff and veterans age, and some unfortunately develop AD, samples of their serum, sequentially collected over the years and held frozen in this collection, could prove invaluable for tracing the immune response to invasion by the AG, and the body's attempts to defend against it.

Be ready for surprise revelations about Alzheimer's

Quite often in infectious disease, when a way is found to visualize or grow a new germ, detect its antigenic fragments or nucleic acid, or the body's antibody reaction to it, the understanding of the organism and the spectrum of its invasiveness changes greatly.

Terminology detour: When a germ invades and causes obvious disease, both laypeople and physicians say that person is "infected". But if that germ enters the body and is destroyed by its defenses without a visible fuss, or survives but is held in check, laypeople see nothing amiss and usually classify that person as "normal" or "uninfected."

However, physicians who find that certain "normal-looking" people have a positive blood test or skin test as immunological evidence that the germ is, or was, within them classify these individuals as also "infected". Thus, laymen can be confused when they find doctors are including some outwardly normal people among the "infected" group.

Sub-clinical infections

A common discovery is that some apparently normal people can yield a positive blood test or skin test, showing that a given germ was, or even is still, inside them. Examples are hepatitis C, TB, latent

syphilis, HIV before AIDS develops, leprosy, typhoid, meningococci, streptococci, chlamydia, Epstein-Barr virus, human papilloma virus, and human polyomaviruses.

If the positive immunological test is interpreted to mean the silent germ presents a current or future danger to the person, treatment will be administered despite lack of symptoms.

Sub-clinical polio

When early epidemiologists investigated polio outbreaks, they found that, as expected, paralyzed polio patients had antibodies to the polio virus.

But to their surprise, so did thousands of apparently normal people who did not recollect having any illness, or maybe just a minor “cold”. Here’s an important point: Less than one-half percent of polio virus infections resulted in visible paralysis. So, judging the presence of a germ only by the obvious disease it produces can greatly undercount the people it has invaded. Thus, the AG might be present in many more people than have AD.

Sub-clinical Zika infection stimulates thinking about AD

Most recently, microcephaly of babies born to Zika-infected pregnant women has been of great concern. Blood tests for antibodies to the Zika virus revealed that 80-90 percent of infections of adults had produced no symptoms that the patient could recall. Even some of the mothers giving birth to stricken babies could remember no symptoms. Not all infected babies have skull abnormalities.

Here’s something to ponder. Researchers are unanimous that Zika virus can enter the fetus’s brain, and survive there. For how long nobody knows. There is evidence it causes not only a misshapen skull, but also damages the baby’s mental function.

Now, suppose that Zika virus infected the pregnant woman and traveled into her fetus, but caused no noticeable symptoms in either. Both would look outwardly normal. But let’s say that Zika virus stayed in the child’s brain, slowly causing damage.

If 70 years later that infant—now aged—developed dementia due to that persistent Zika, the examining neurologist would have no idea the disastrous process could be due to the long-ago acquisition of Zika virus. The patient would have no history nor memories of a Zika infection, and the mother, long dead, recognized no prenatal infection. Because of such theoretical scenarios, we must include in our research the possibility that a long-forgotten or unnoticed infection from childhood—such as Zika—has smoldered on, resulting in AD in later life.

Germ carriers may not show illness themselves

Sometimes the germ itself is found sitting on accessible surfaces, or within, a person, not causing any harm (“carriers”). But, it can travel from them to a more susceptible individual and cause a deadly

infection. Examples: Meningococci resting quietly in your throat can cause meningitis when transmitted to another, and staphylococci residing in your nose can travel to infect somebody else's surgical wound. Many women carrying the gonococcus have no idea they harbor it, but their germ can cause a symptomatic infection in their male partner. Ditto chlamydia, HPV, herpes, and others.

Early infections can become dormant and erupt years later

A current neurological disease may turn out to be a late manifestation of an earlier agent thought long gone from the person. Example: shingles breakouts in adults (herpes zoster) are reactivations of childhood chickenpox that stayed dormant in the patient's nerves for decades.

Syphilis infecting young adults initially creates a small sore at the point the germ enters, then a brief rash. Then it "goes silent", but in up to 30 percent of untreated patients can emerge decades later as neurosyphilis, the brain affliction which destroyed Winston Churchill's father.

An attack of polio survived in childhood may, 30-40 uneventful years later, cause post-polio syndrome in a percentage of cases, with loss of nerve function leading to disability.

Thus, the AG may turn out to "infect" many people early in life, but in most of those it could remain silent, and cause no problem in later life. In only a fraction of cases will it progress, as infected people age, to what we see as AD.

What if many "normal people" have antibodies to the Alzheimer's germ?

Be prepared for some surprises when a new blood test is evaluated for detecting a person's immunological response to infection by the AG.

Yes, it should be positive in 80 to 90 percent of patients having advanced disease and residing in Alzheimer care facilities. (I do not say 100 percent, because some serious dementias diagnosed as Alzheimer's may actually be caused by some other process that produces similar symptoms. The blood test will help clarify that).

But, what if positive results, indicating previous or current germ presence, are also found in blood samples from thousands of normal-appearing siblings, relatives, friends, caregivers, and in some members of the general population?

Science progress may reshape our understanding of AD. It could turn out that the AG invades many, but only a few develop the characteristic brain damage. Remember that most people infected with the polio virus—as determined by blood tests—do not exhibit paralysis. Similar "silent" infections, revealed only by immunological tests, are found with Zika and tuberculosis.

Whether a positive blood test, as a person's only sign of infection by the AG, will ever lead to loss of brain function will have to be determined by longitudinal studies. If the findings with many other

microorganisms prove applicable, the answer is nothing further will happen to many individuals whose blood test is reactive.

So, if many people, or even most, are infected by the theorized AG, why do only some develop what we now label as “Alzheimer’s disease”, with concomitant disastrous loss of mental function? A key factor will be variations in human susceptibility to the AG germ.

Alzheimer’s gene research revealing susceptibility, not cause?

Many AD research projects are directed at genetics in one way or another. Virtually all these hope to shed light on, or even pin down, precisely how certain genes contribute to a theorized “cause” of AD, such as amyloid plaques or protein tangles.

The weakness in ascribing Alzheimer’s completely to genetics was demonstrated in the largest study of identical twins, 12,000 pairs. In the cases of male twins where one or both developed AD, 55 percent of the time one of the pair had not developed it—despite sharing identical genes with the sibling.

However, in this “new germ” theory of AD, the genetic findings take on a completely different meaning. They are not illuminating any “cause” of Alzheimer’s; instead, they are revealing which genetic patterns and mutations increase a person’s susceptibility to the AG. This hypothesized germ, in susceptible people, takes hold and proceeds to cause brain damage and byproducts, such as amyloid tangles, and inflammation.

Conversely, when humans infected with the AG do not develop Alzheimer’s disease, which I believe is most people whom the germ enters, we may assume their genetics enables them to control AGs which enter their bodies, and thus they resist progression to brain damage.

Genes can influence susceptibility to other infections

The role of genetics in susceptibility to germs and development of damage has been made quite clear by research on other diseases. For example, of all people exposed to the tubercle bacillus only a few develop clinical tuberculosis. Several genes have been spotlighted as responsible for this resistance.

Gene influence on susceptibility has also been flagged in leprosy, fungal infections, Lyme disease, leishmaniasis, toxoplasma, syphilis, HIV, malaria, influenza, and other infections. Even kuru, a paralyzing prion infection—as some believe AD to also be—has been reported to be blocked by a particular gene mutation.

Thus, for genetic and other reasons, most people infected by many other germs keep those under control and do not develop clinically-evident damage. It is therefore likely the same phenomenon is occurring with the AG; the unfortunate patients who develop dementia could be only a fraction of the humans the AG has entered.

Could AD germs transmitted through semen mimic genetics?

Men infected with Zika or HIV can transmit those viruses via semen or sperm to female partners. If the resultant infection enters the fetus but is silent for years, its harmful effects on the child's brain during adult life can produce disease. This could be wrongly attributed to genetic factors from the parents. In like fashion, the AG could be transmitted through semen or sperm, create effects years later, and thus create the misleading appearance of genetic factors at work causing AD.

How to increase funding for Alzheimer's germ research

Basically, there are only two ways to fund a more intense search for the AG: Increase the overall Alzheimer's research budget, or re-prioritize some portion of currently planned allotments.

The solution most palatable to the research community would be increasing overall funding even further. However, most governments, the major source of research monies, are coping with tight budget scenarios. Moreover, in the U.S. there have recently been significant additional funds targeted to AD research; by some calculations the current total is in excess of \$2.3 billion—a record amount. There are already those who say more money alone is not the answer.

Recently, private philanthropy has increased its role. As noted previously, Bill Gates has allocated \$50 million for research, and \$50 million for venture philanthropy. Other donors have also promised significant amounts.

Alternatively, couldn't some of the presently contemplated government or private monies be re-prioritized, so as to immediately fund studies to find and elucidate the AG?

Problem: No scientist will admit his or her project is of lower priority than someone else's.

The existing peer review committees that rank Alzheimer's research grant proposals are not the best arbiters for the readjustments required. After all, most of these review scientists are themselves, in their own research, often heavily financed by what have been the major funding allocations so far—amyloid plaques, tau tangles, genetics, and “big data”. (These subjects can now be dubbed the “Conventional Wisdom Quartet.”). Thus, many of these judges have a scientific and financial conflict of interest, i.e. an open or subconscious bias against recognizing a priority need for grants to search for an AG.

Are large funds and staffs always needed?

In the U.S. alone, federal funding this year for AD research will be about \$2.3 billion.

But note: Big sums and lots of workers have never been proven necessary to pinpoint the cause of other infectious diseases of great public health importance. Usually the discovery was made by one talented person, or a few, in their own existing lab, inspired by curiosity or routine duties.

In recent decades, Joseph McDade discovered the bacterium causing Legionnaire's disease using his already-existing CDC lab. Barry Marshall and Robin Warren discovered *H. pylori*, the cause of gastric ulcers and more, despite few resources and little outside funding. And HIV was pinpointed as the cause of the AIDS epidemic by Robert Gallo, not in the National Institute of Allergy and Infectious Diseases, but in the NIH's National Cancer Institute. Oh, he used his existing lab staff and resources.

Wikipedia lists 217 "infectious diseases." If you check their history, you will find most were discovered by one person, in modest settings, with little additional funding. Some of these successes followed a dedicated, exhausting search, and some came through luck or accident. So, the AG might be found on the cheap, by one curious, committed scientist, working in his or her existing laboratory, with little or no extra funding. Perhaps you, the reader?

Certainly, there will be times when lengthy, expensive research, by teams of scientists, is the only way a medical mystery can be solved. But this is often the not the case when it comes to finding important new germs.

The opioids of Alzheimer's research: Lifestyles and risk factors

If one germ is responsible for AD, as I believe, the vast monies being spent researching Alzheimer's patients' "lifestyles" and "risk factors" will provide interesting but not crucial information. No result of such studies can guarantee you will or won't get AD. These studies are, in a sense, opioids and tranquilizers to soothe the public demand that "something" be done about AD.

There is only one crucial research item missing at this time: The root cause of AD. By this I mean the initial trigger. Unless it is pulled, nothing will happen. If the AG is absent, AD will not develop, no matter what else goes on.

Tuberculosis provides an analogy. Malnutrition, inhaling coal dust, weak lungs, crippled immune defenses, and working with untreated TB patients will all increase your chances of getting TB. But nothing happens, regardless of risk factors or lifestyle, unless the tubercle bacillus enters your body and incites tuberculosis.

Few infectious disease specialists investigate Alzheimer's

Illnesses classified as "epidemics" or "outbreaks" attract a lot of research professionals in certain specialties. The big three of these are infectious diseases, microbiology and epidemiology. So, if the root cause of Alzheimer's is—or even could be—a germ, why are there so few of these particular specialists involved in researching it?

Main problem: AD is classified as only a "chronic disease". Less drama, less attention. The patients sicken and die slowly. And they are mostly seniors—a group whose ailments don't seem to inspire media attention comparable to those of babies (Zika) or young adults (HIV/AIDS). Because there's

been no cause identified, or cure, the disease seems intractable, and thus has become largely tolerated as part of the “customary” medical and public health background.

Another challenge: Alzheimer’s is intertwined with neurology. And not many neurologic-focused illnesses intersect with infectious disease and microbiology. [A few which do: Guillian-Barre syndrome from vaccines or Zika, shingles from the flareup of childhood chickenpox (herpes zoster) virus dormant in nerves, and viral or bacterial meningitis.]

Final hurdle: No curative medicine. Few physicians have the desire, or temperament, to devote their professional works to patients who, at this time, seem doomed to die a slow death, regardless of what the doctor does.

However, the large and rising annual body count of Alzheimer’s victims surpasses that of any national epidemic in recent memory. For example, in 2015 there were 52,404 U.S. deaths from the well-publicized “opioid emergency”, but AD caused more than twice as many, 110,561. So, it is clearly the country’s top unsolved and untreatable epidemic.

Pleas of Alzheimer’s research experts ignored so far

Here’s the peculiar situation. In 2016, 33 of the top Alzheimer’s researchers who, despite few grants manage to keep alive interest in infection, pleaded—in an editorial in the Journal of Alzheimer’s Disease—for more financial support for research on an infectious cause of the disease. But though they have great talents in many pertinent areas, most are not especially known for their expertise in detection and control of infectious diseases of public health importance. Thus, their entreaties seemed to produce little growth of financial support for research in this niche.

Conversely, the infectious disease and public health communities—which have vast experience searching for dangerous germs of all sorts—are preoccupied with their own favorite subjects, which do not include a non-febrile chronic disease with years-long decline of brain function as the main symptom, and no simple diagnostic test, and no cure.. Thus, few infectious disease specialists, public health microbiologists, or epidemiologists, have taken an interest in AD so far.

What would trigger action by the infectious disease community?

For germ detectives, the hot buttons today which guarantee funds and community support are fevers and body counts. Think Ebola, SARS, AIDS, Zika, swine flu, hepatitis, and superbugs.

In other words, show the infectious disease professionals a dangerous and fast-acting scourge fitting the classic picture of an infectious disease, and they’re on it full force, no holds barred. Government labs snap to attention, and research grants appear like magic. Usually world-class success is obtained, and the threat is eliminated or contained.

But if a mystery condition is not considered to be typically infectious, few infectious disease clinicians, microbiologists, public health workers, government agencies, or foundations will seek an as-yet-undetected causative bacterium, virus, prion, or parasite.

How different from the earliest decades of infectious disease, when almost every sickness that could be examined was tested to possibly reveal germs. Low budget. And it paid off. Finding the TB bacillus showed the disease wasn't caused by inheritance. Identifying the organisms of cholera and typhoid replaced strange theories about those diseases. Similarly, it was found that malaria wasn't caused by swamp vapors, nor polio by filth or crowds.

Key U.S. groups are the Infectious Diseases Society of America (I am an emeritus fellow) and the American Society of Microbiology. Their journals and meetings so far convey little interest in AD. The situation is the same for similar groups in other countries.

Thus, there is little or no collaboration between the groups most knowledgeable about AD research and those most experienced in research on other diseases now accepted as infectious.

Infectious disease society now offers grants

An encouraging sign: recently the U.S.'s principal organization for infectious diseases specialists, the Infectious Diseases Society of America, has offered through its Foundation two small seed grants for research focused on AD. Though the initial amount of money is relatively small, the greater significance is that experts in traditional infectious diseases now consider AD a suitable target for investigation. Hopefully, larger funders of AD research will now follow this initiative.

Current federal classifications hinder Alzheimer's germ detection

The two most pertinent U.S. agencies that deal with urgent infection mysteries—the federal Centers for Disease Control and Prevention (CDC) and National Institute of Allergy and Infectious Diseases (NIAID)—must also get busy, not just through requests for proposals or offering long-term grants but also by immediate intramural acquisition and exploration of blood and tissue samples already accessible.

The primary U.S. government overseer of billions of dollars of AD research grants is the NIH's National Institute on Aging (NIA). It houses, and makes grants to, many top researchers. However, though on the same campus as NIAID, it does not have the experience, repertoire, or grantee network of that institute for ferreting out an infectious cause of AD. Instead, it has committed almost its entire \$2 billion budget and staff to the conventional Big Four: amyloid plaques, tau tangles, genetics, and "big data".

At CDC, studies of AD are consigned to the chronic disease units, are mostly compilations of statistics, and are not investigated as possible microbiological phenomena. In contrast, outbreaks of

other mystery illnesses classified as “acute” are handled by the well-known “germ detectives” unit, the Epidemic Intelligence Service (EIS), and supporting laboratories.

Why the “\$1 Million Alzheimer’s Germ” challenge award?

To professionals with an interest in infectious diseases and some knowledge of their spectrum of presentations and peculiarities, it is a startling experience to delve into the research literature on AD. Many of the patterns, observations, and data one finds are strikingly similar to certain patterns found in well-accepted, but not common, infections.

But these provocative clues have been little explored. More investigation must be undertaken promptly. Only in that way can a possible AG be uncovered if it is there.

Cognizant of such sayings as “Better to light a candle than to curse the darkness”, we (I and my wife) formed a public benefit corporation, Alzheimer’s Germ Quest, Inc., to assess gaps in knowledge and stimulate grant funding in this obviously underfunded research niche.

Also, having read about the success of “challenge awards” in bringing forth research accomplishments in some other science and business areas, we decided to create one for this particular search. Therefore, we set up the “\$1 Million Alzheimer’s Germ Quest Challenge Award,” for the scientist who provides persuasive evidence that a particular infectious agent is the root cause or trigger of AD.

A secondary aim of the Challenge Award is to increase public and research awareness of the rather neglected—but likely important—niche of infectious triggers for AD. Hopefully, more research funders will be motivated to target increased grants to this promising search.

Scientists should register for the Challenge Award by submitting the form at:

<https://alzgerm.org/scientists-preliminary-expression-interest>. **(No monetary donations are sought or accepted.)*

Benefits of finding the “Alzheimer’s Germ”

Detecting a germ that triggers AD will allow medical and public health experts to finally control and defeat the epidemic. Applied research scientists can then develop simple diagnostic tests, applicable to blood, urine, breath or stool samples. And compounds to kill or halt the organism can be found or designed; many precedents exist in the fields of antibacterial and anti-viral chemistry. And, if those approaches do not prove effective, it may be possible to create a vaccine to at least prevent future cases. As a last resort, barrier precautions and disinfection protocols may be needed.

Conclusion: New actions needed

Despite the seriousness of AD, a rising number of cases, and billions of dollars spent on research, no cause or cure has been found. Infectious agents, the cause of many other damaging neurological afflictions, have not yet been exhaustively sought and examined, though both classic and newer methods are readily available. There is now much circumstantial evidence that one or more germs, known or yet unknown, may be the root cause, or trigger, for AD.

The unfortunate chasm between current Alzheimer's research programs and the resources of infectious disease experts, microbiologists, and public health laboratories has delayed the necessary critical investigations. It is urgent to assemble a unified task force, cooperatively combining openminded, pertinent professionals and techniques for the required studies.

Also, a useful portion of existing allotments must be re-prioritized. For example, if a modest ten percent of the current U.S. one-year Alzheimer's research budget of \$2.3 billion were to be redirected to illuminating the AG, that would create focused grant funds of \$230 million.

Final thought

This quest to find the Alzheimer's germ may or may not succeed, but failing to search thoroughly guarantees we find nothing □

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Originally posted online January 15, 2018

Updated September 2, 2018

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