

A photograph of a female doctor in a white lab coat and blue scrubs, wearing white gloves, administering a vaccine to an elderly male patient's arm. The doctor is looking down at the patient's arm. The patient is an older man with a beard, wearing a light-colored shirt. The background is a clinical setting with a white wall and a small potted plant. The image is overlaid with a semi-transparent dark grey filter.

SHINGLES VACCINATION REDUCES RISK OF ALZHEIMER'S AND PARKINSON'S DISEASE

STEVEN LEHRER, MD

PETER H. RHEINSTEIN, MD, JD, MS

PRESENTERS

Steven Lehrer, MD
Icahn School of Medicine
Mount Sinai Medical Center
New York, New York 10029
steven.lehrer@mssm.edu

Peter H. Rheinstein, MD, JD, MS
621 Holly Ridge Road
Severna Park, Maryland 21146
phr@severnhealthsolutions.com

FLU AND PNEUMONIA VACCINATION REDUCE RISK OF ALZHEIMER'S DISEASE (AD)

- Infectious diseases might confer a risk of AD [13]. Protection against bacterial and viral infection is beneficial to the brain.
- 5.1% (n = 47,889) of flu-vaccinated patients and 8.5% (n = 79,630) of flu-unvaccinated patients developed AD during 46-month follow-up [1].
- Being vaccinated against pneumonia between ages 65-75 was associated with a reduction in the risk of AD afterwards (OR = 0.70; P < 0.04) in logistic model with all covariates. Largest reduction in the risk of AD (OR = 0.62; P < 0.04) was observed in the vaccinated against pneumonia non-carriers of rs2075650 G allele (risk factor for AD) [2].

HERPES SIMPLEX TYPE 1 (HSV-1) AND HERPES ZOSTER VIRUS (HZV) MAY INTERACT TO TRIGGER AD

- Herpes Zoster virus may activate dormant Herpes Simplex Type 1 virus [3].
- Herpes Simplex Type 1 virus is implicated in the development of AD [4].
- HSV-1 can produce neuroinflammation, which is associated with an increased risk of developing Alzheimer's disease. Inflammation is linked to aging and many age-related disorders. Chronic, sterile, low-grade inflammation, known as **inflammaging**, develops as people age and is linked to age-related disorders such as Alzheimer's disease, cerebrovascular disease, and diminishing adaptive immunity.
- Beta-amyloid in AD is antimicrobial and an inherited defense against HSV-1 [12].

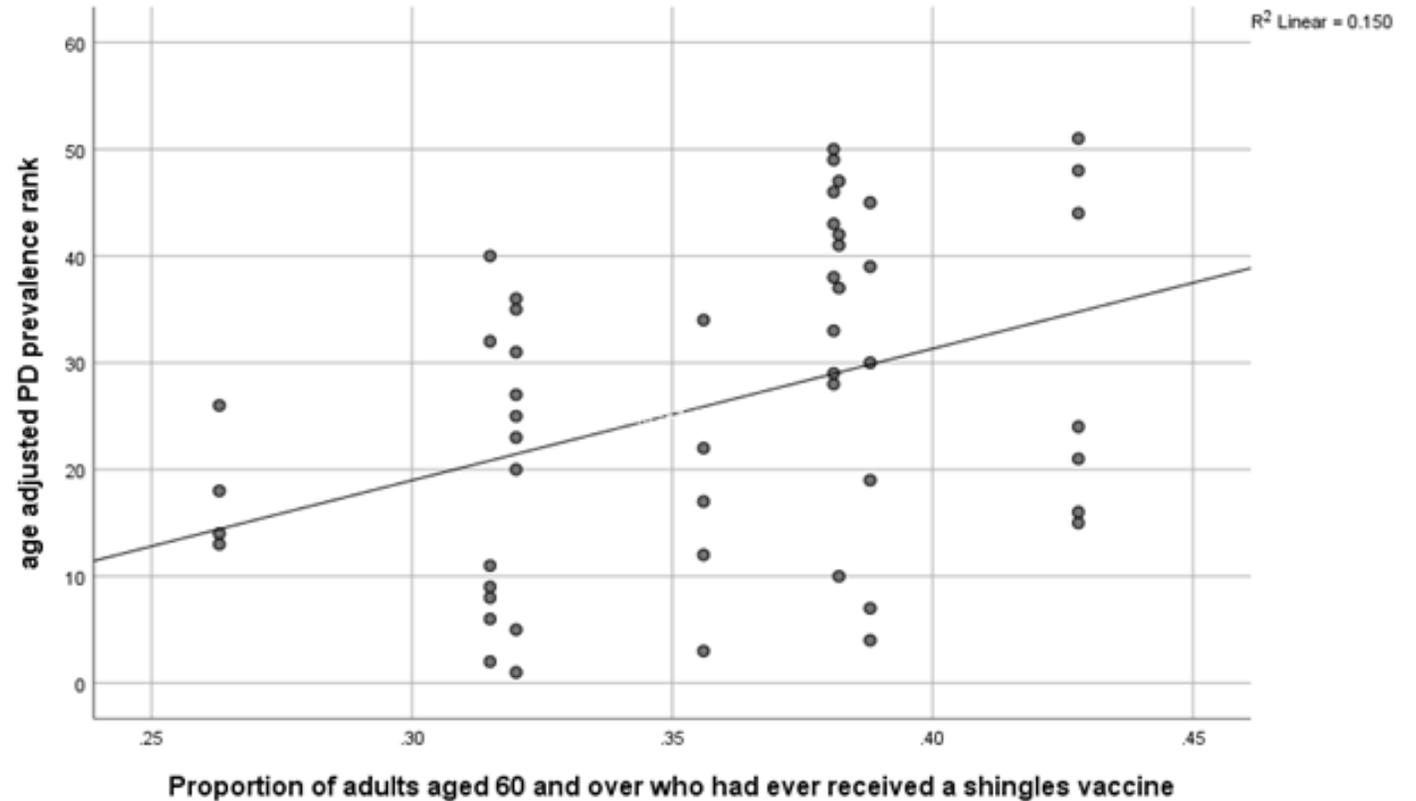


SHINGLES VACCINE ZOSTAVAX REDUCES RISK OF AD

- Lehrer and Rheinstein (2021) found a 15% dementia risk reduction in vaccinated subjects. Our finding that shingles vaccination reduces the risk of dementia is consistent with the link between viruses and AD. Herpes virus-induced reactivation of embryologic pathways silenced at birth could be one of the pathologic processes in Alzheimer's disease [5].
- Lophatananon et al (2021) found a 20% AD risk reduction in vaccinated subjects [6].
- Schnier et al (2022) found reduced dementia incidence after varicella zoster vaccination in Wales 2013–2020. Vaccinated individuals were at reduced risk of dementia (adjusted hazard ratio: 0.72; 95% confidence interval: 0.69 to 0.75) [11].
- Unanswered question: Are the AD-risk-reducing effects of flu, pneumonia, and shingles vaccination cumulative?

SHINGLES VACCINATION REDUCES RISK OF PARKINSON'S DISEASE (PD)

- US States with the most PD (lowest age adjusted prevalence ranks) had the lowest proportion of adults aged 60 and over who had ever received shingles vaccine ($p = 0.005$). States with the highest prevalence of PD are defined to be states with the lowest prevalence ranks of PD.
- Steven Lehrer, Peter H. Rheinstein. Shingles vaccination reduces risk of Parkinson's disease. medRxiv 2022.07.18.22277767; doi: <https://doi.org/10.1101/2022.07.18.22277767>



AD AND PD MAY BE DUE TO EMBRYOLOGIC REACTIVATION OF PROCESSES AND PATHWAYS SILENCED AT BIRTH

- Neuroinflammation is associated with cytokines and growth factors in AD. Cytokines and neurotrophins have a significant impact on PD and Lewy Body Dementia (LBD) as well. Growth factors, neurotrophins, and cytokines are also involved in the development of the embryonic brain. In the preimplantation embryo, cytokines affect gene expression, metabolism, cell stress, and death. Around the time of birth, the genes that cause these changes are silenced. However, they could ruin the same neuronal structures they formed in utero if reactivated in the brain by inflammation (inflammaging) and viruses decades later.
- GBA, BIN1, APOE, SNCA, and TMEM175 are five genes that have a role in determining whether a person will develop LBD, and some of these genes are also linked to AD and PD. AD, PD, and LBD lie on a continuum in vulnerable persons [5].



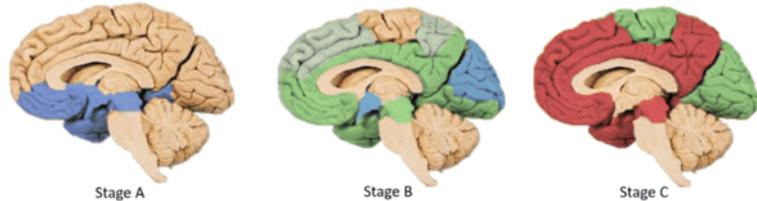
AD AND PD EMBRYOLOGIC REACTIVATION IS SUGGESTED BY THEIR PROGRESSION

- AD and PD do not spread willy-nilly within the brain. They progress in a predictable fashion, the Braak stages. AD and PD represent a complex physiologic process gone awry.
- The advanced Braak stages V and VI are almost identical in AD and PD. In their advanced stages AD and PD are difficult to distinguish clinically from one another.

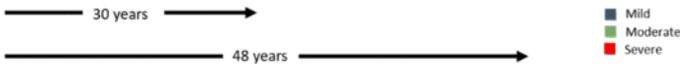
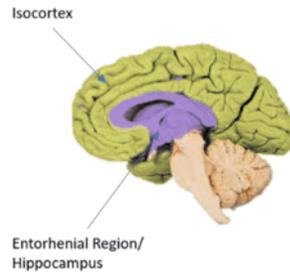
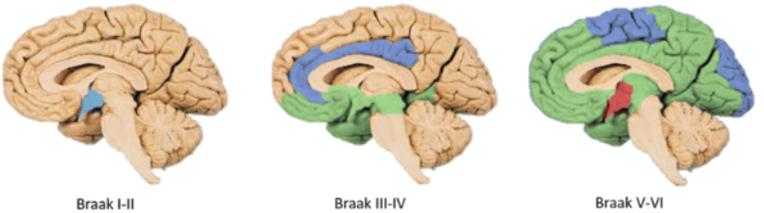
AD AND PD EMBRYOLOGIC REACTIVATION SUGGESTED BY THEIR CHARACTERISTIC PROGRESSION, THE BRAAK STAGES

Alzheimer's Disease [9]

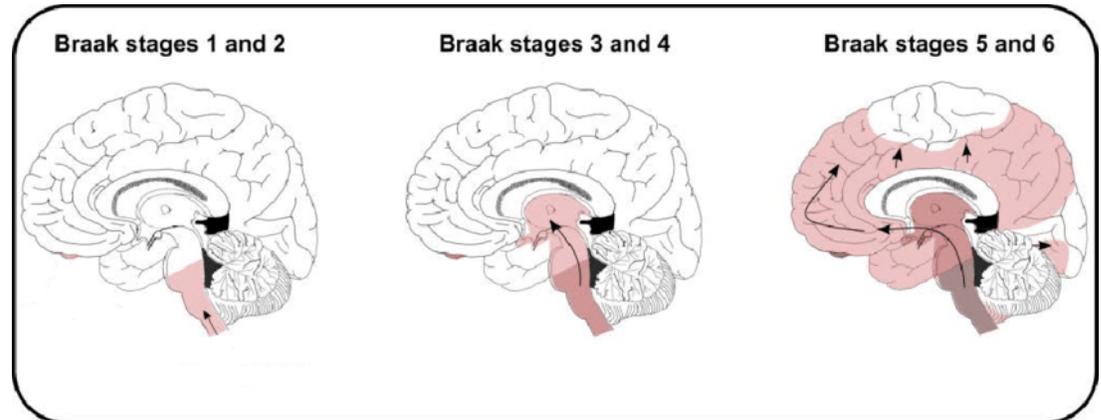
Amyloid Plaque Stages



Tau Braak Stages



Parkinson's Disease [10]



FOUR CHARACTERISTICS OF ALZHEIMER'S DISEASE COULD BE EXPLAINED BY EMBRYOLOGIC REACTIVATION.

- *NSAIDs (non steroidal anti-inflammatory drugs) lessen the risk of Alzheimer's disease but are ineffective as a therapy.* NSAIDs lessen the risk of Alzheimer's disease by suppressing inflammation. They are not, however, a cure because they are unable to silence the embryonic genes that have become active and are causing brain damage.
- Children with fetal alcohol syndrome (FAS) have abnormal performance in learning and memory activities, which are assumed to be linked to the hippocampus, and some FAS children have abnormal hippocampal anatomy. In an age-dependent manner, light to moderate wine drinking appears to lessen the risk of dementia and cognitive decline. *Alcohol disrupts the embryology of a fetus's developing brain, lowering IQ. However, alcohol may interfere with embryologic reactivation in the elderly, lowering the chance of Alzheimer's disease.*
- Within days of undergoing low-dose radiation treatment, patients with severe Alzheimer's disease showed significant improvement in behavior and cognition. But ionizing radiation has a significant negative impact on the growing brain, IQ, and learning capacity.
- The inconsistent association between herpes viruses and Alzheimer's disease could be because herpes viruses are not a direct cause of the disease. The likelihood of embryologic reactivation and gene un-silencing is increased by herpes viruses.



GENE SILENCING AND REACTIVATION CONTROLLED BY HISTONES

- The nucleus of every cell has two meters of DNA. To create chromatin, nucleosomes made up of eight histone proteins are first wrapped around the DNA. The tails of histones carry chemical modifications such as methylation, acetylation, and ubiquitylation, while nucleosomes also carry information about spacing. These alterations, or marks, tell the cells which genes to express and which to silence. Numerous proteins, along with remodelers and chaperones, have evolved to write, read, and remove the histone marks [7].



WHY IS ADVANCING AGE THE GREATEST RISK FACTOR FOR AD?

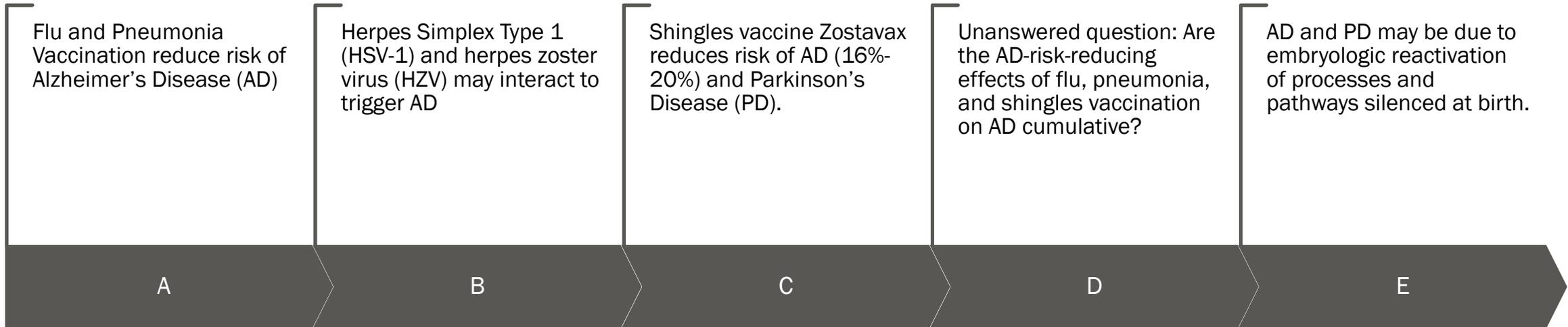
- Chemical modifications carried by the tails of histones--methylation, acetylation, and ubiquitylation--silence genes. But the modifications are not bolted on with iron bands. Chemical forces hold them in place until the end of reproductive life. Thereafter evolution is indifferent as to what happens to them. With advancing age, the chemical modifications are dislodged by viruses, infections, and inflammaging. Embryologic pathways and processes silenced at birth are reactivated. AD, PD and other forms of neurodegeneration are the result.
- Cancer is an analogue. Cancer is a disease of aging. Many cancers develop after an accumulation of genetic mutations that occur with age.



EMBRYOLOGIC REACTIVATION IS UNSTOPPABLE

- Once embryologic reactivation has occurred in the brain of an older person and AD or PD develop, this complex process relentlessly destroys what it created in utero.

SUMMARY





SLIDES AVAILABLE FROM FERMATA PHARMA WEBSITE

- Download slides from <http://fermatapharma.com>

REFERENCES

- [1] Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE (2022) Risk of Alzheimer's Disease Following Influenza Vaccination: A Claims-Based Cohort Study Using Propensity Score Matching. *Journal of Alzheimer's Disease* **88**, 1061-1074.
- [2] Ukraintseva S, Yashkin A, Duan M, Akushevich I, Arbeev K, Wu D, Stallard E, Tropsha A, Yashin A (2020) Repurposing of existing vaccines for personalized prevention of Alzheimer's disease: Vaccination against pneumonia may reduce AD risk depending on genotype. *Alzheimer's & Dementia* **16**, e046751.
- [3] Cairns DM, Itzhaki RF, Kaplan DL (2022) Potential Involvement of Varicella Zoster Virus in Alzheimer's Disease via Reactivation of Quiescent Herpes Simplex Virus Type 1. *Journal of Alzheimer's Disease* **88**, 1189-1200.
- [4] Itzhaki RF (2021) Overwhelming Evidence for a Major Role for Herpes Simplex Virus Type 1 (HSV1) in Alzheimer's Disease (AD); Underwhelming Evidence against. *Vaccines (Basel)* **9**.
- [5] Lehrer S, Rheinstein PH (2021) Herpes Zoster Vaccination Reduces Risk of Dementia. *In Vivo* **35**, 3271-3275.
- [6] Lophatananon A, Mekli K, Cant R, Burns A, Dobson C, Itzhaki R, Muir K (2021) Shingles, Zostavax vaccination and risk of developing dementia: a nested case-control study-results from the UK Biobank cohort. *BMJ Open* **11**, e045871.
- [7] Grau-Bove X, Navarrete C, Chiva C, Pribasnig T, Anto M, Torruella G, Galindo LJ, Lang BF, Moreira D, Lopez-Garcia P, Ruiz-Trillo I, Schleper C, Sabido E, Sebe-Pedros A (2022) A phylogenetic and proteomic reconstruction of eukaryotic chromatin evolution. *Nat Ecol Evol* **6**, 1007-1023.
- [8] Steven Lehrer, Peter H. Rheinstein. Shingles vaccination reduces risk of Parkinson's disease. medRxiv 2022.07.18.22277767 <https://doi.org/10.1101/2022.07.18.22277767>
- [9] Swarbrick S, Wragg N, Ghosh S, Stolzing A (2019) Systematic Review of miRNA as Biomarkers in Alzheimer's Disease. *Molecular Neurobiology* **56**, 1-12.
- [10] Georgiopoulos C (2019) Imaging Studies of Olfaction in Health and Parkinsonism.
- [11] Schnier C, Janbek J, Lathe R, Haas J (2022) Reduced dementia incidence after varicella zoster vaccination in Wales 2013–2020. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* **8**, e12293.
- [12] Lehrer S, Rheinstein PH (2020) Alignment of Alzheimer's Disease Amyloid-beta Peptide and Herpes Simplex Virus-1 pUL15 C-Terminal Nuclease Domain. *J Alzheimers Dis Rep* **4**, 373-377.
- [13] Sochocka M, Zwolinska K, Leszek J (2017) The Infectious Etiology of Alzheimer's Disease. *Curr Neuropharmacol* **15**, 996-1009.

Introductory photo credit: Getty Images