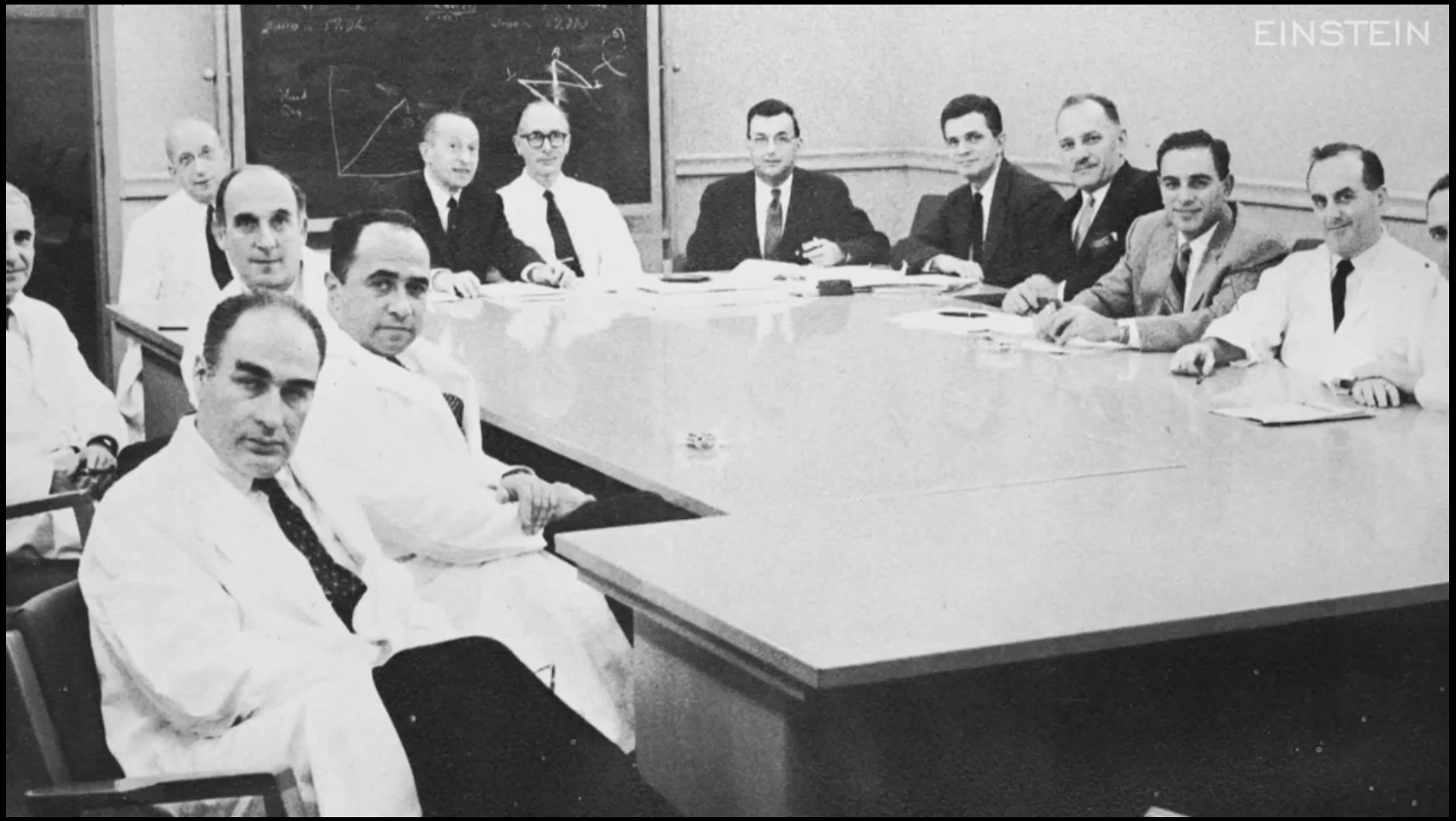
AANP 2014:
Dr. Saul Korey Lecture

Alzheimer's Disease & Related Dementias: Policy and Progress

Thomas J. Montine, MD, PhD
Alvord Professor & Chair
Department of Pathology
University of Washington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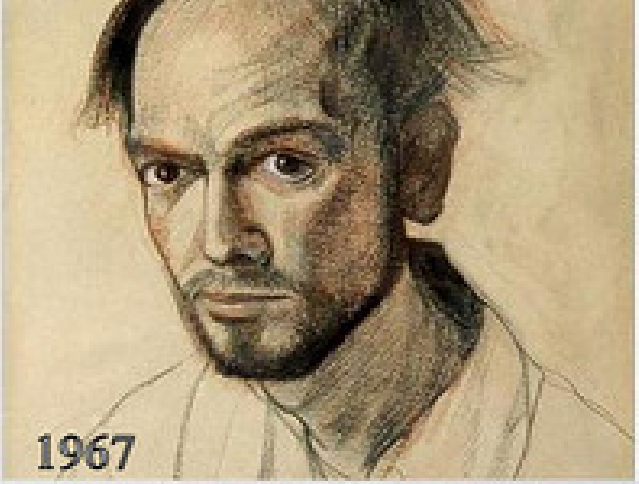
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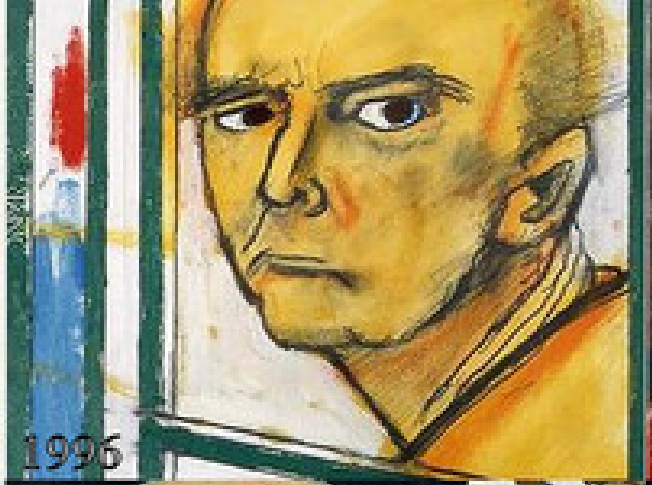
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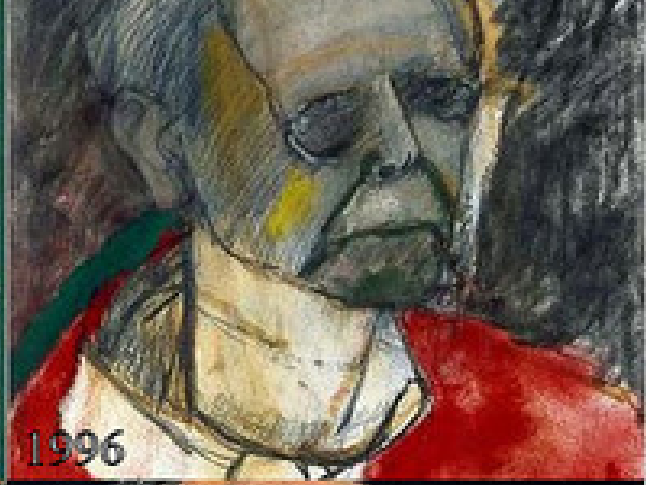
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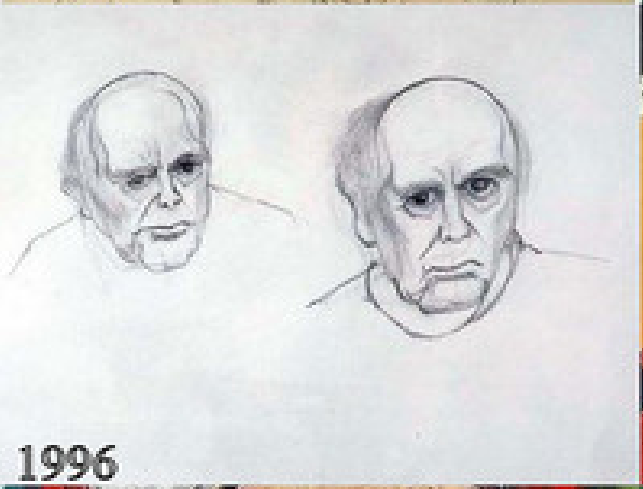
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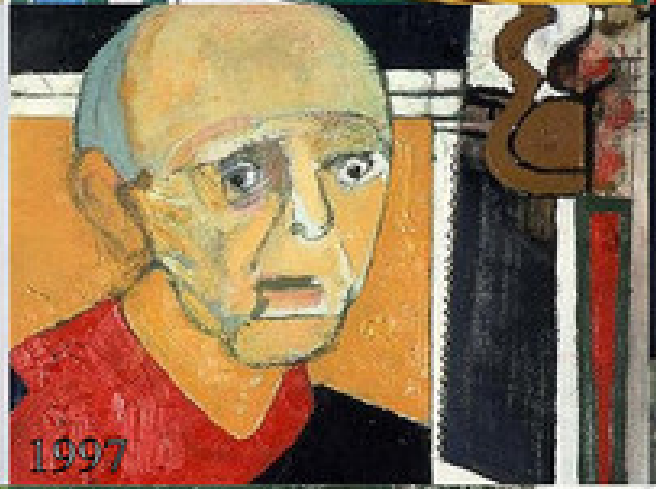
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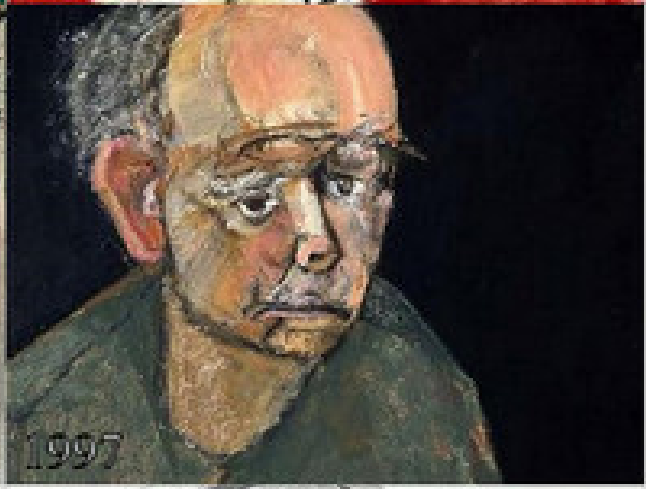
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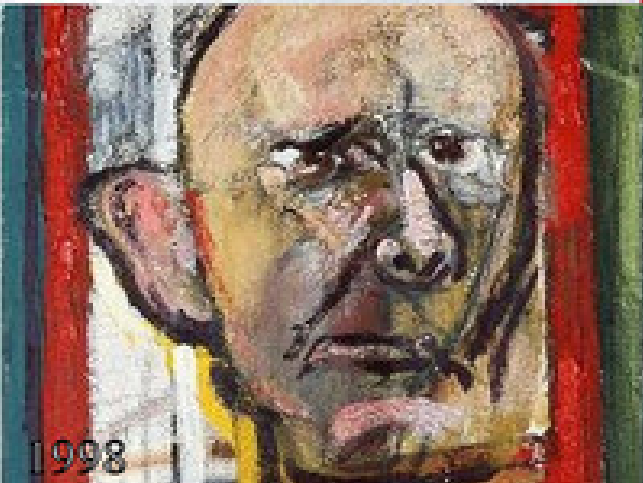
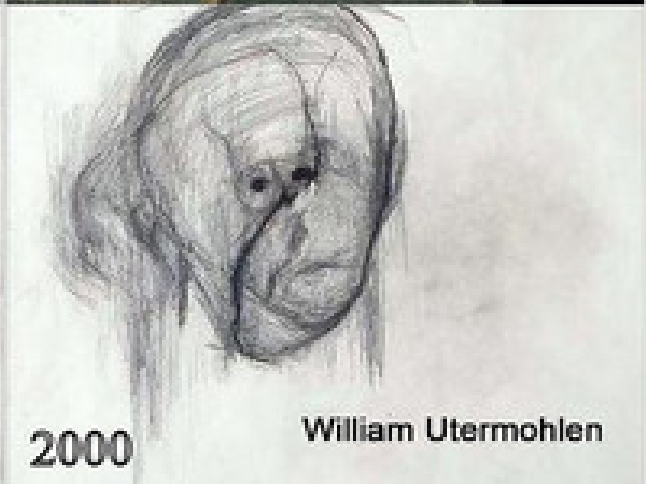
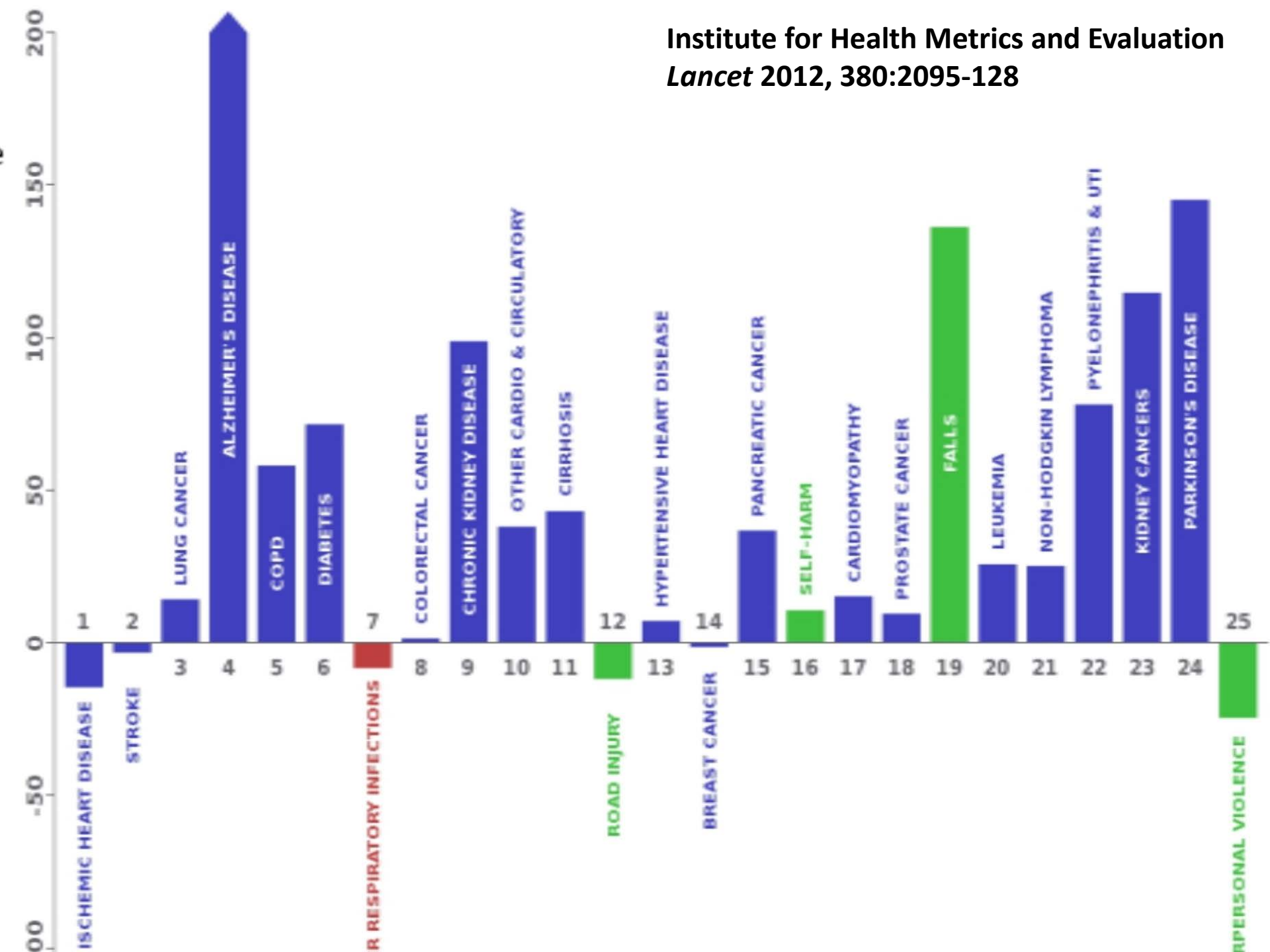

1998


1999

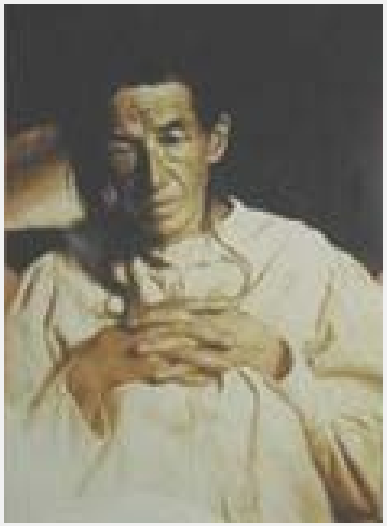

2000
William Utermohlen

Institute for Health Metrics and Evaluation
***Lancet* 2012, 380:2095-128**



National Alzheimer's Project Act (NAPA)

- **Signed into law by President Obama**
  - **January 2011**
- **National Plan to Address Alzheimer's Disease**
  - **"Preventing and effectively treating Alzheimer's disease, including Alzheimer's disease–related dementias, by 2025"**

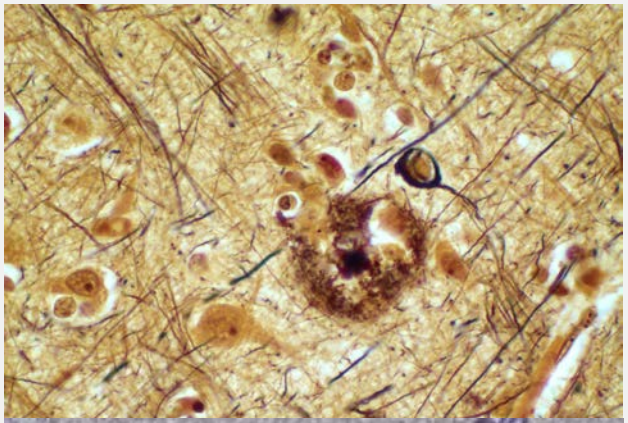


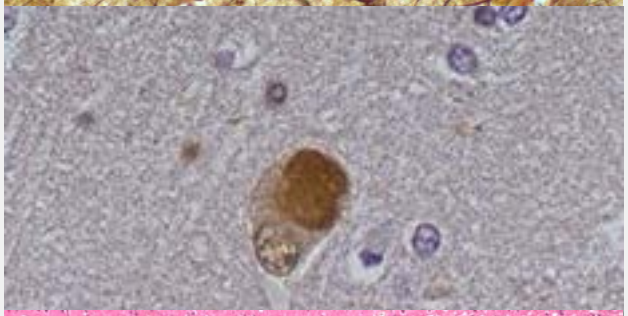
Scientific and Medical Input to NAPA

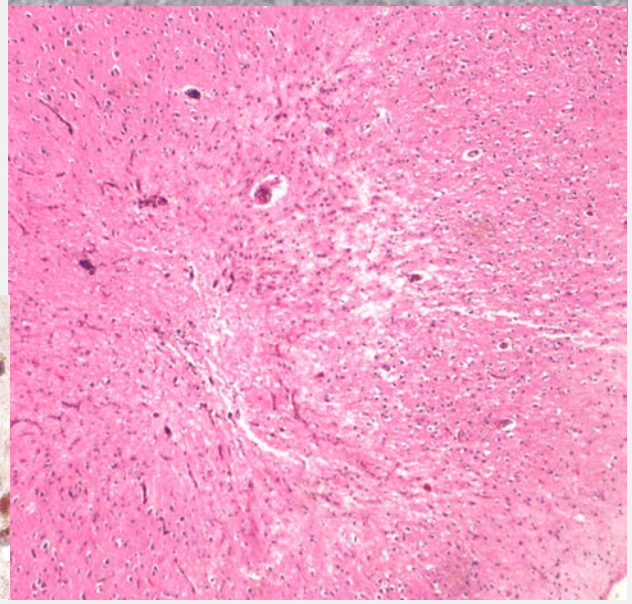
- ***Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention***
  - http://www.nia.nih.gov/about/events/2012/alzheimers-disease-research-summit-2012-path-treatment-and-prevention
- ***Alzheimer's Disease–Related Dementias: Research Challenges and Opportunities***
  - http://www.ninds.nih.gov/ADRD2013
  - **Neurology, *in press***

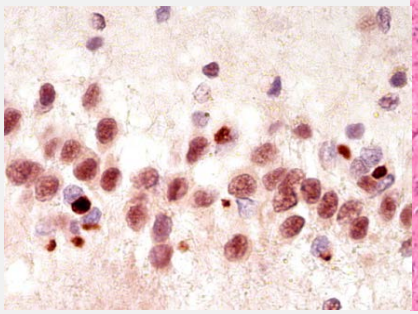
Cognitive Impairment and Dementia

- **Syndrome**
- **In older adults …**
  - **An idiosyncratic convergent trait**
    - **AD, VBI, LBD, HS**
  - **Caused by chronic diseases**
    - **Dementia**
    - **Prodrome**
    - **Latency**
- **In middle-aged adults**
  - **Less co-morbidity**
  - **AD, FTD, LBD**









AD Research Summit 2012

- **AD dementia**
  - G. McKhann (B. Hyman). 709 Citations
  - Alzheimer's & Dementia 2011;7:263-269
- **Mild Cognitive Impairment due to AD**
  - M. Albert (D. Dickson). 653 Citations
  - Alzheimer's & Dementia 2011;7:270-279
- **Toward defining preclinical stages of AD**
  - R. Sperling (T. Montine). 1098 citations
  - Alzheimer's & Dementia 2011;7:280-292
- **Guidelines for neuropath assessment of AD**
  - B. Hyman and T. Montine
  - Alzheimer's & Dementia 2012;8:1-13. 165 citations
  - Acta Neuropathol. 2012;123:1-11. 139 citations

2012 Guidelines for neuropath assessment

- Thomas G. Beach
- Eileen H. Bigio
- Nigel J. Cairns
- Dennis W. Dickson
- Charles Duyckaerts
- Matthew P. Frosch
- Bradley T. Hyman
- Eliezer Masliah
- Suzanne S. Mirra
- Thomas J. Montine
- Peter T. Nelson
- Creighton H. Phelps
- Julie A. Schneider
- Dietmar Rudolf Thal
- John Q. Trojanowski
- Harry V. Vinters

Major Changes to NP Assessemnt

Issue	1997	2012
Dx of dementia required for NP AD	Yes	No
NP assessment	Braak stage and CERAD score	These plus Thal phase
Common co-morbid diseases	Little guidance	Explicit
Minimum regions	Silent	Explicit
Reporting and CPC	Silent	Guidelines

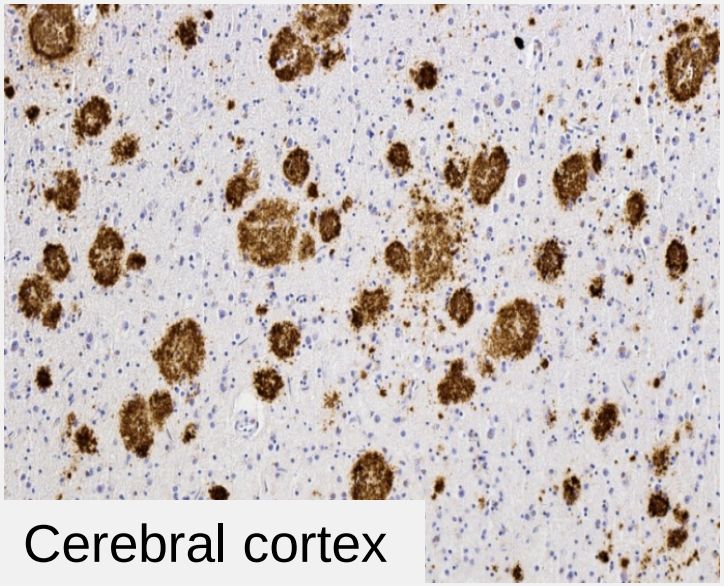
Region x Stain

	AD Neuropathologic Change		
	A	B	C
Region	**Stain for A! /amyloid plaques [57]**	**Stain for NFTs [14,15]**	**Stain for NPs [41]**
Medulla including DMV			
Pons including LC			
Midbrain including SN	**3º: if 2º is +**		
Cerebellar cortex and dentate n.	**3º: if 2º is +**		
Thalamus and subthalamic n.[1]			
Basal ganglia at level of AC with basal nucleus of Meynert[1]	**2º: if 1° is +**	Consider[4]	
Hippocampus and EC[1]	**2º: if 1º is +[2]**	**Yes**	Consider[4]
Cingulate, anterior			
Amygdala			
Middle frontal gyrus[1]	**1º [2]**	**Yes**	**Yes**
Superior & middle temporal gyri[1]	**1º [2]**	**Yes**	**Yes**
Inferior parietal lobule[1]	**1º [2]**	**Yes**	**Yes**
Occipital cortex (BA 17 & 18)[1]	Consider[4]	**Yes**	Consider[4]
WM at ACA, MCA, and PCA watershed			

AD Neuropathologic Change

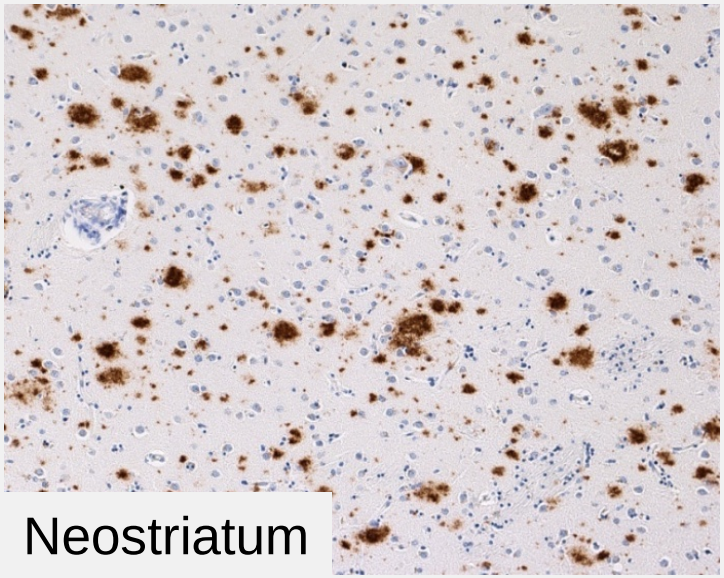
"A"	Thal Phase for A! plaques [57]	"B"	Braak and Braak NFT Stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

AD Neuropathologic Change		B[1]		
A[2]	C[3]	0 or 1	2	3
0	0	Not[4]	Not[4]	Not[4]
1	0 or 1	Low	Low	Low[5]
	2 or 3[7]	Low	Intermediate	Intermediate[5]
2	Any C	Low[6]	Intermediate	Intermediate[5]
3	0 or 1	Low[6]	Intermediate	Intermediate[5]
	2 or 3	Low[6]	Intermediate	High

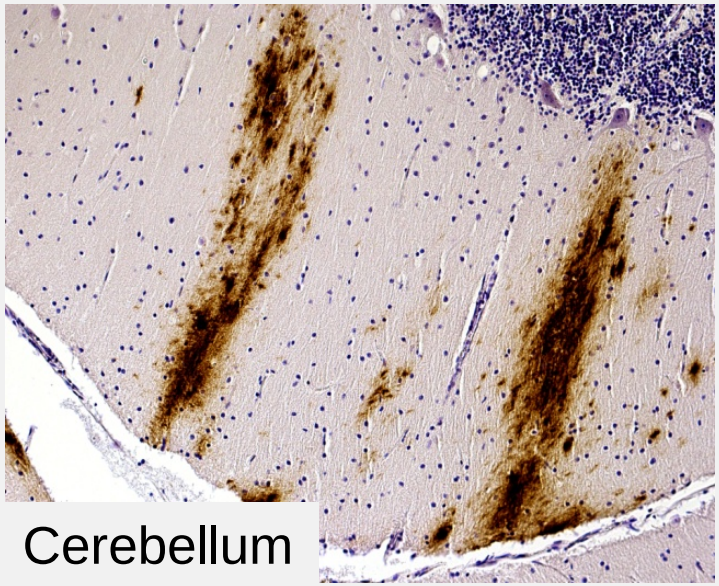


Cerebral cortex

A (amyloid) Score

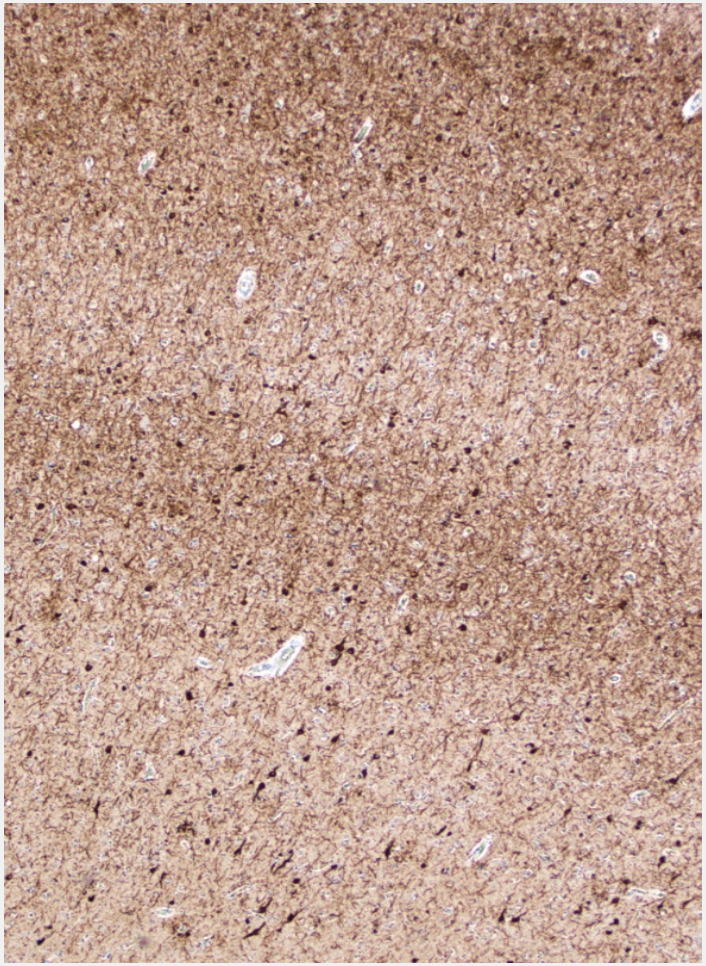


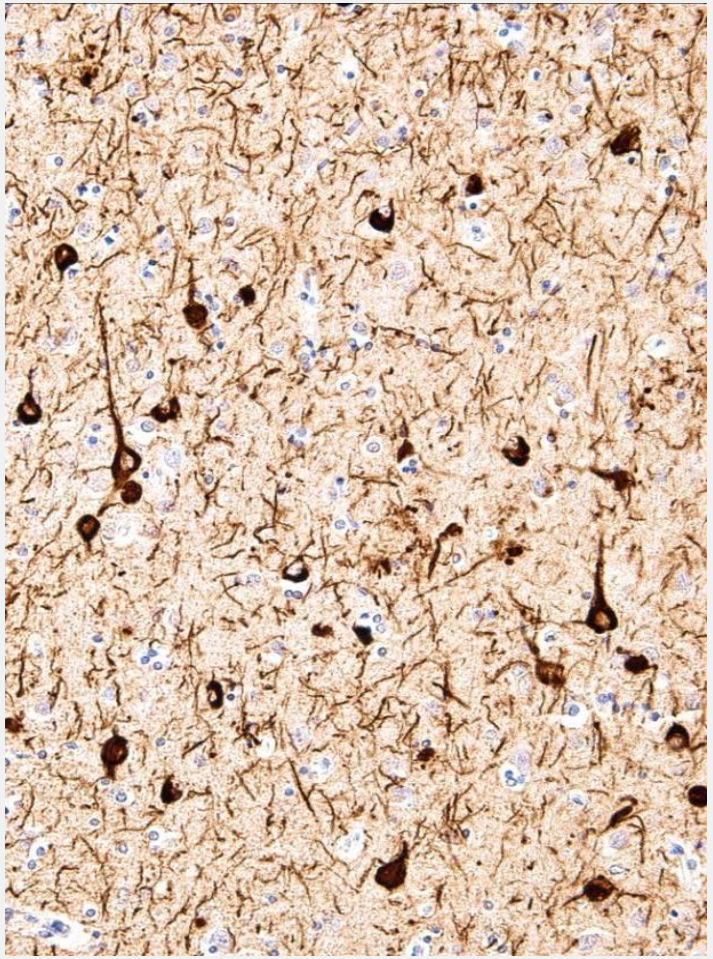
Neostriatum



Cerebellum

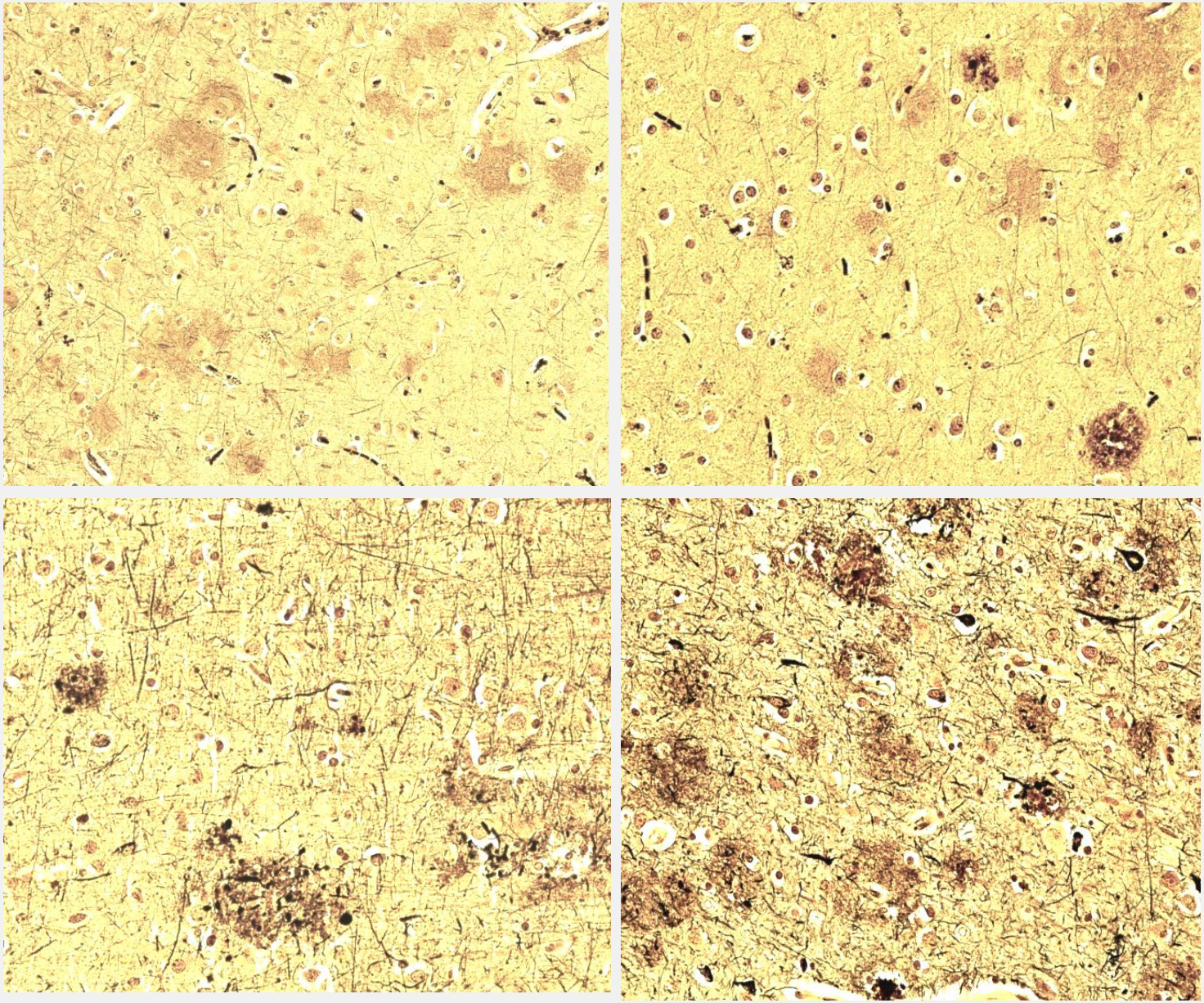
B (Braak) Score in primary visual cortex





PHF-1 antibody was generously provided by Dr. Peter Davies

C (CERAD) Score in neocortex



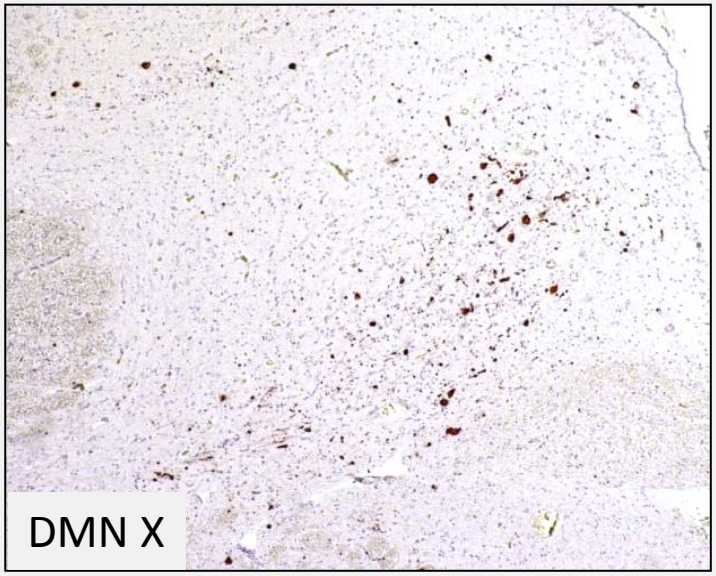
Region x Stain

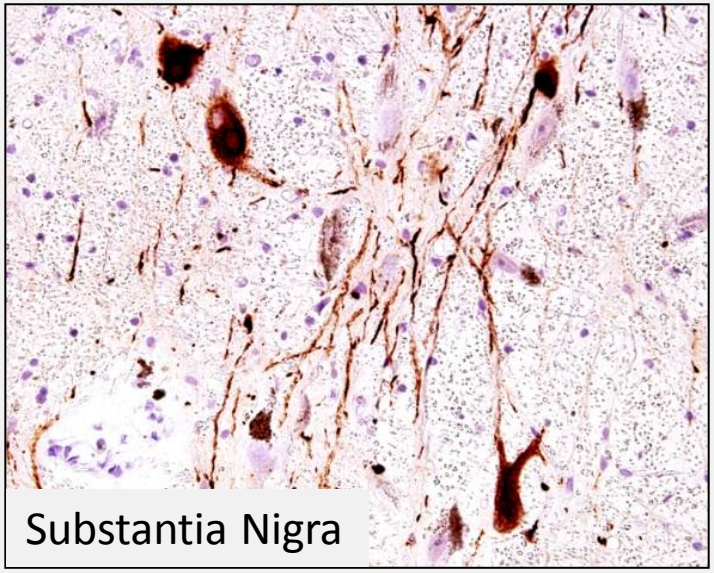
	AD Neuropathologic Change			LBD
	A	B	C	
Region	Stain for A! /amyloid plaques [57]	Stain for NFTs [14,15]	Stain for NPs [41]	**Stain for LBs**
Medulla including DMV				**1º: IHC or H&E[3]**
Pons including LC				**1º: IHC or H&E[3]**
Midbrain including SN	3º: if 2º is +			**1º: IHC or H&E[3]**
Cerebellar cortex and dentate n.	3º: if 2º is +			
Thalamus and subthalamic n.[1]				
Basal ganglia at level of AC with basal nucleus of Meynert[1]	2º: if 1º is +	Consider[4]		
Hippocampus and EC[1]	2º: if 1º is +[2]	Yes	Consider[4]	**2º: IHC in at least one if 1º +**
Cingulate, anterior				
Amygdala				**1º: IHC[3]**
Middle frontal gyrus[1]	1º [2]	Yes	Yes	**2º: IHC in at least one if 1º +**
Superior & middle temporal gyri[1]	1º [2]	Yes	Yes	
Inferior parietal lobule[1]	1º [2]	Yes	Yes	
Occipital cortex (BA 17 & 18)[1]	Consider[4]	Yes	Consider[4]	
WM at ACA, MCA, and PCA watershed				

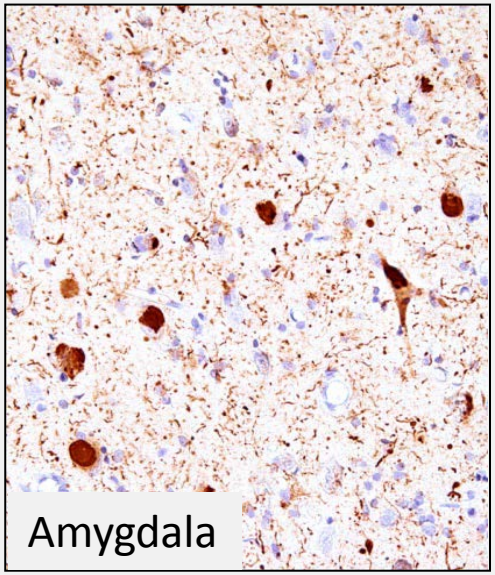
Lewy Body Disease

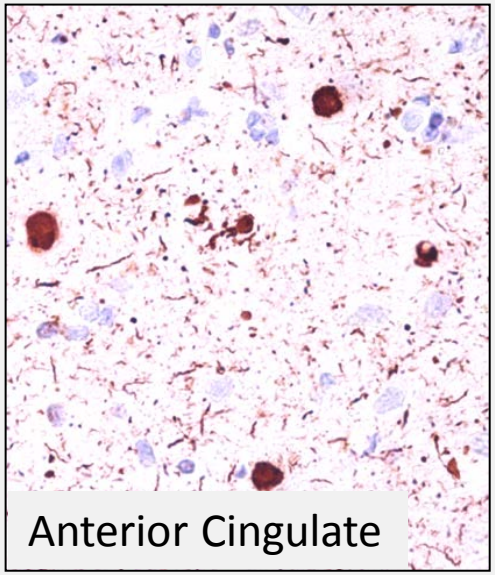
None	No LBs or related changes in IHC for ″ -synuclein
Brainstem-predominant	LBs in medulla, pons, or midbrain
Limbic (Transitional)	LBs in cingulate or entorhinal cortices, usually with brainstem involvement
Neocortical (Diffuse)	LBs in frontal, temporal, or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala
Amygdala-predominant	LBs in amygdala with paucity of LBs in the above regions

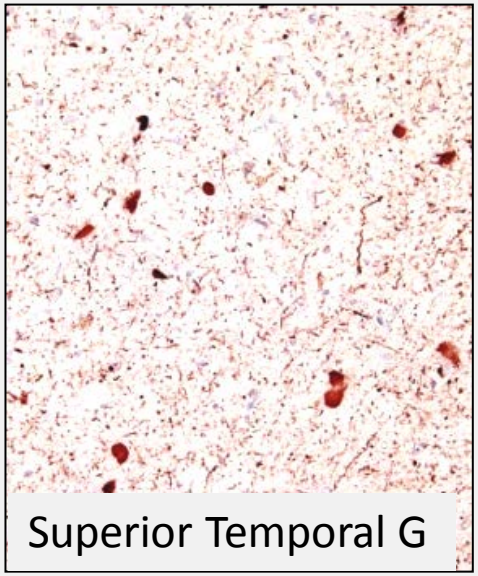
Lewy Body Disease











Anti-alpha-synuclein antibody KM51 (Novocastra, Newcastle, United Kingdom)

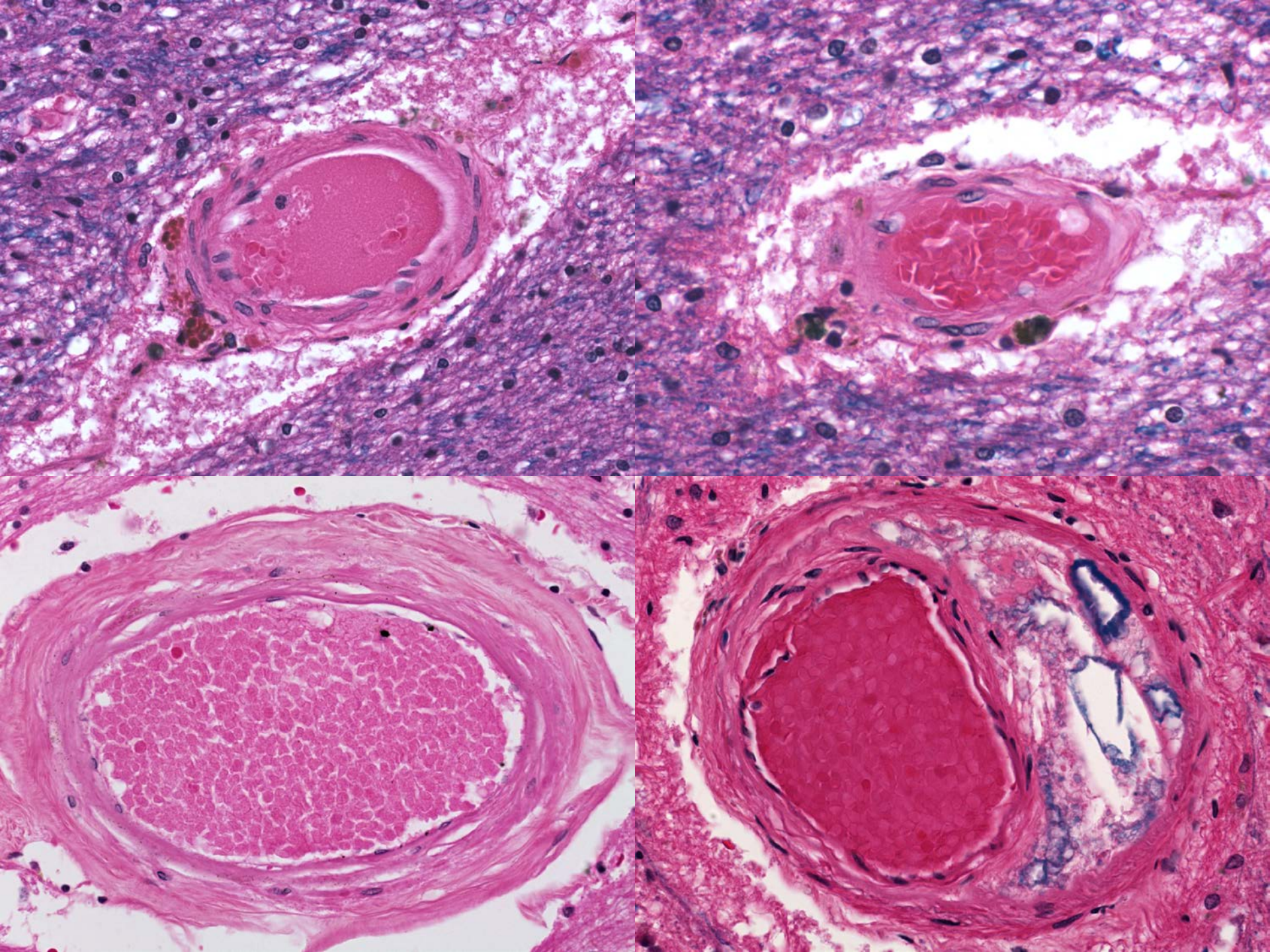
Region x Stain

	AD Neuropathologic Change			LBD	VBI & HS
	A	B	C		
Region	Stain for A! /amyloid plaques [57]	Stain for NFTs [14,15]	Stain for NPs [41]	Stain for LBs	**H&E**
Medulla including DMV				1º: IHC or H&E[3]	VBI
Pons including LC				1º: IHC or H&E[3]	VBI
Midbrain including SN	3º: if 2º is +			1º: IHC or H&E[3]	VBI
Cerebellar cortex and dentate n.	3º: if 2º is +				VBI
Thalamus and subthalamic n.[1]					**MVL**
Basal ganglia at level of AC with basal nucleus of Meynert[1]	2º: if 1º is +	Consider[4]			**MVL**
Hippocampus and EC[1]	2º: if 1º is +[2]	Yes	Consider[4]	2º: IHC in at least one if 1º +	**HS**
Cingulate, anterior					VBI
Amygdala				1º: IHC[3]	VBI
Middle frontal gyrus[1]	1º [2]	Yes	Yes	2º: IHC in at least one if 1º +	**MVL**
Superior & middle temporal gyri[1]	1º [2]	Yes	Yes		**MVL**
Inferior parietal lobule[1]	1º [2]	Yes	Yes		**MVL**
Occipital cortex (BA 17 & 18)[1]	Consider[4]	Yes	Consider[4]		**MVL**
WM at ACA, MCA, and PCA watershed					Consider[4]

Cerebrovascular Disease and Vascular Brain Injury

- **CVD**
  - **Report using standardized approach**

- VBI
  - Record size and location of gross infacrts
  - Enumerate microinfarcts in standard screening sections
    - > 2 sufficient to explain cognitive impairment



Cerebrovascular Disease and Vascular Brain Injury

- CVD
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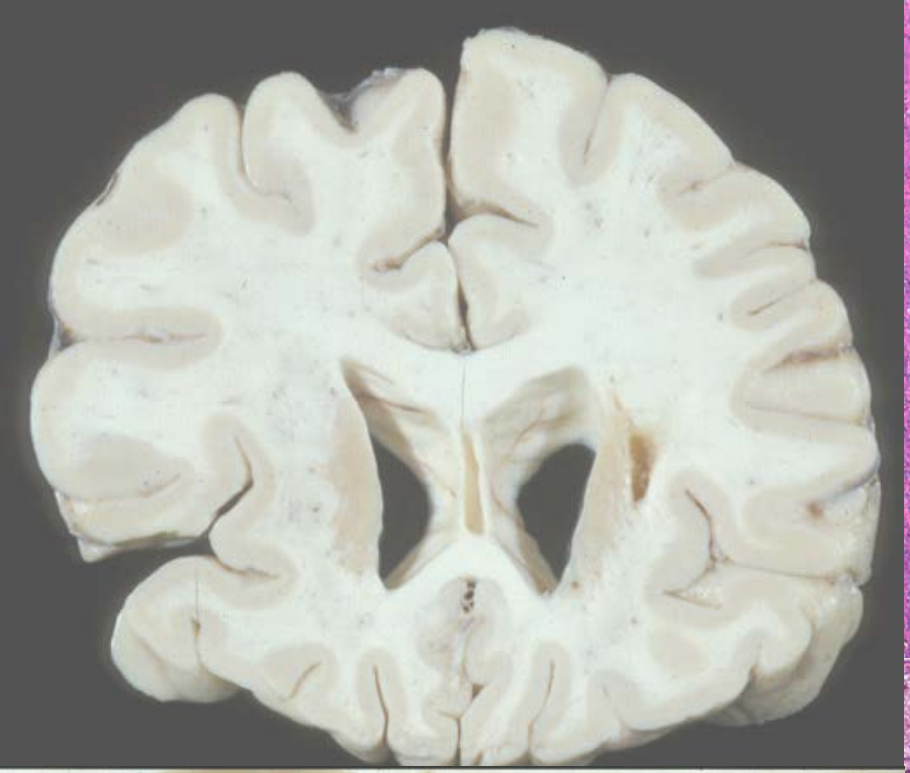
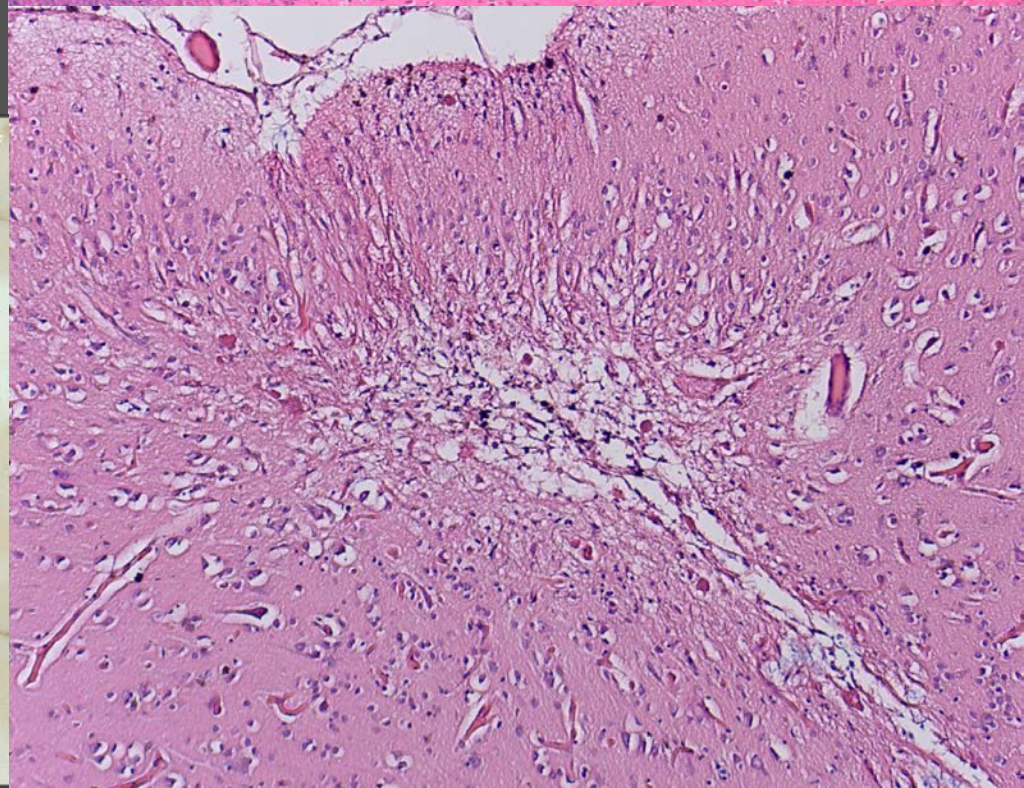
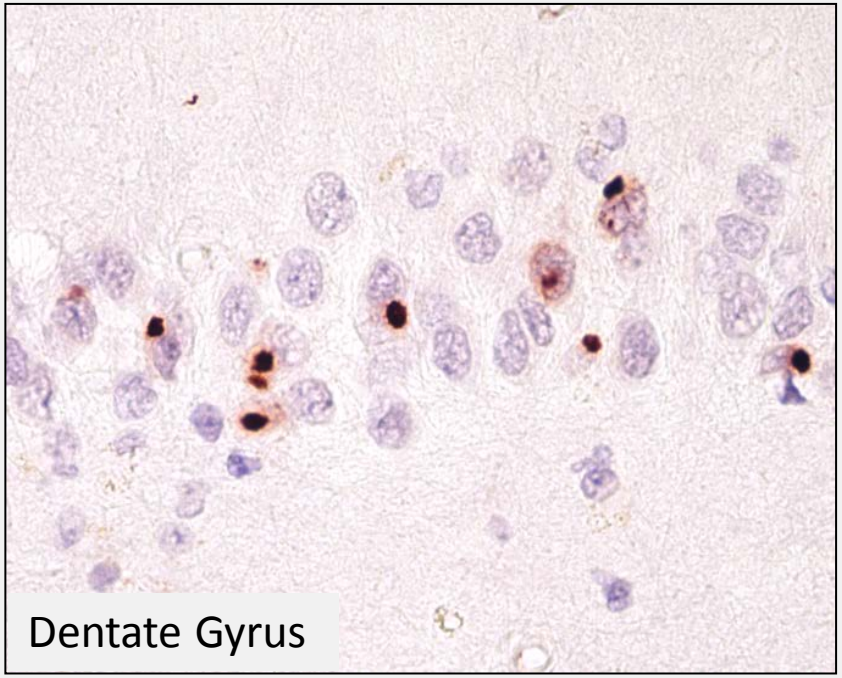




Other common lesions

- **Hippocampal sclerosis**
  - **Present or absent**
- **TDP-43 Inclusions**
  - **Screen in AD cases with Hip Sclerosis**
  - **Present or absent**



Anti-phospho-TDP-43 was antibody TIP-PTD-M01 (pS409/410-1 from Cosmo Bio, Tokyo, Japan)

Reporting

- **Protocol developed for autopsy brain**
  - **Also report in surgical pathology specimens**
- **All neuropathologic lesions and scoring**
  - **Integrate into a clinico-pathologic assessment for each individual**
- **National Alzheimer's Coordinating Center Neuropathology Form v10**

Major Challenges Remain

- **Almost all of our knowledge about dementia in the US comes from people of European decent**
- **Incomplete knowledge about disease mechanisms**
  - **Knowledge about potential interactions is very limited**
  - **AD VBI meeting held by AA**
- **Representative experimental models are needed to fuel therapeutic discovery**

Next Steps …

- **Spring 2014**
  - ADRD recommendations and priorities accepted without revision by NAPA Council
  - Milestones now being finalized
- **October 2014**
  - Report on performance characteristics of the new guidelines
  - NIA NACC project
- **9-11 February 2015**
  - AD Research Summit II
- **Winter 2016**
  - ADRD II
- **2025**
  - "Preventing and effectively treating Alzheimer's disease, including Alzheimer's disease–related dementias", NAPA

Neuropathologists need to contribute their unique expertise

Thank you

For the great honor of delivering the 2014 Dr. Saul Korey Lecture

To all who have worked on developing policy and neuropath guidelines