CERE-110 for Alzheimer's Disease
RECOMBINANT DNA ADVISORY COMMITTEE (RAC)
March 11, 2004

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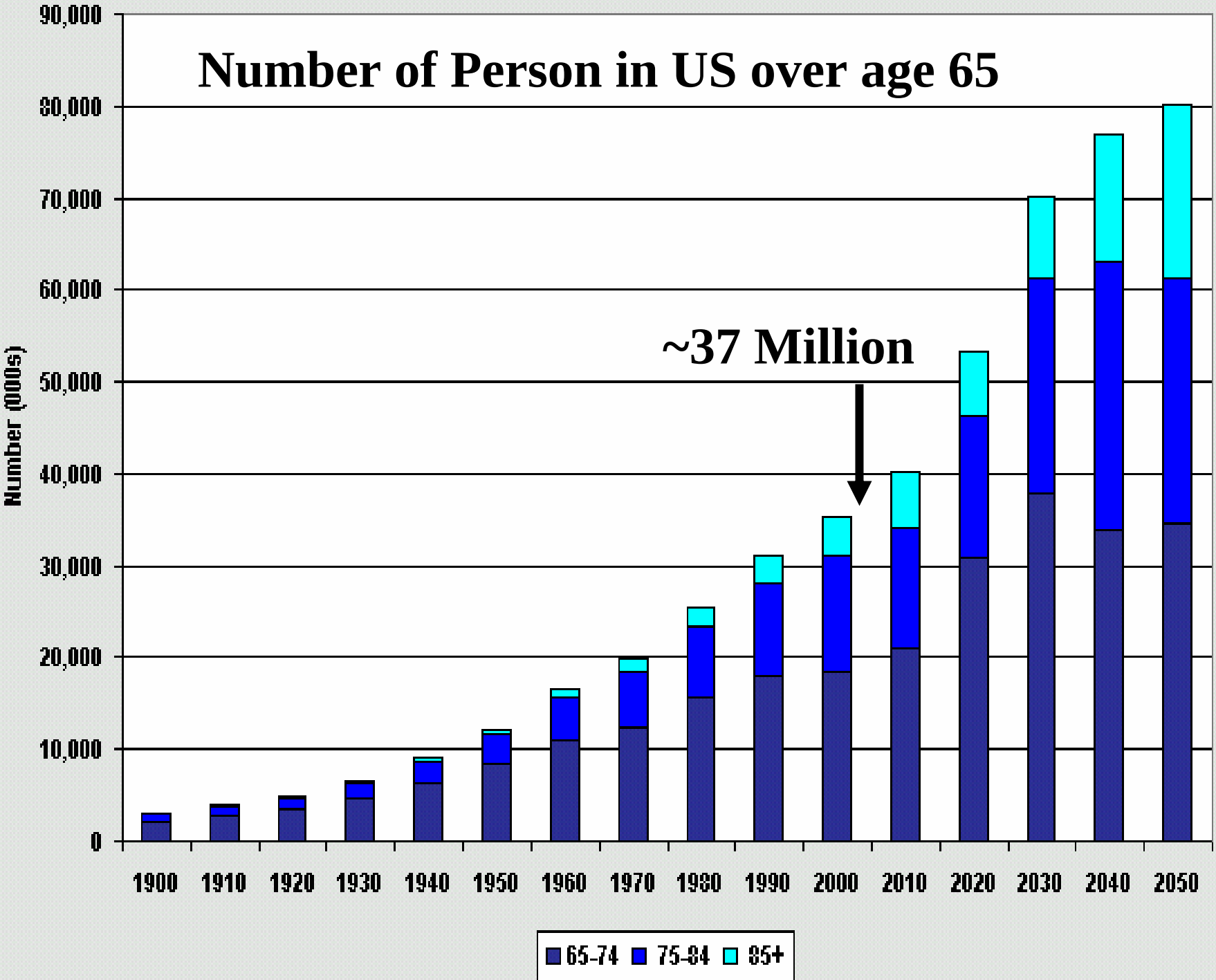
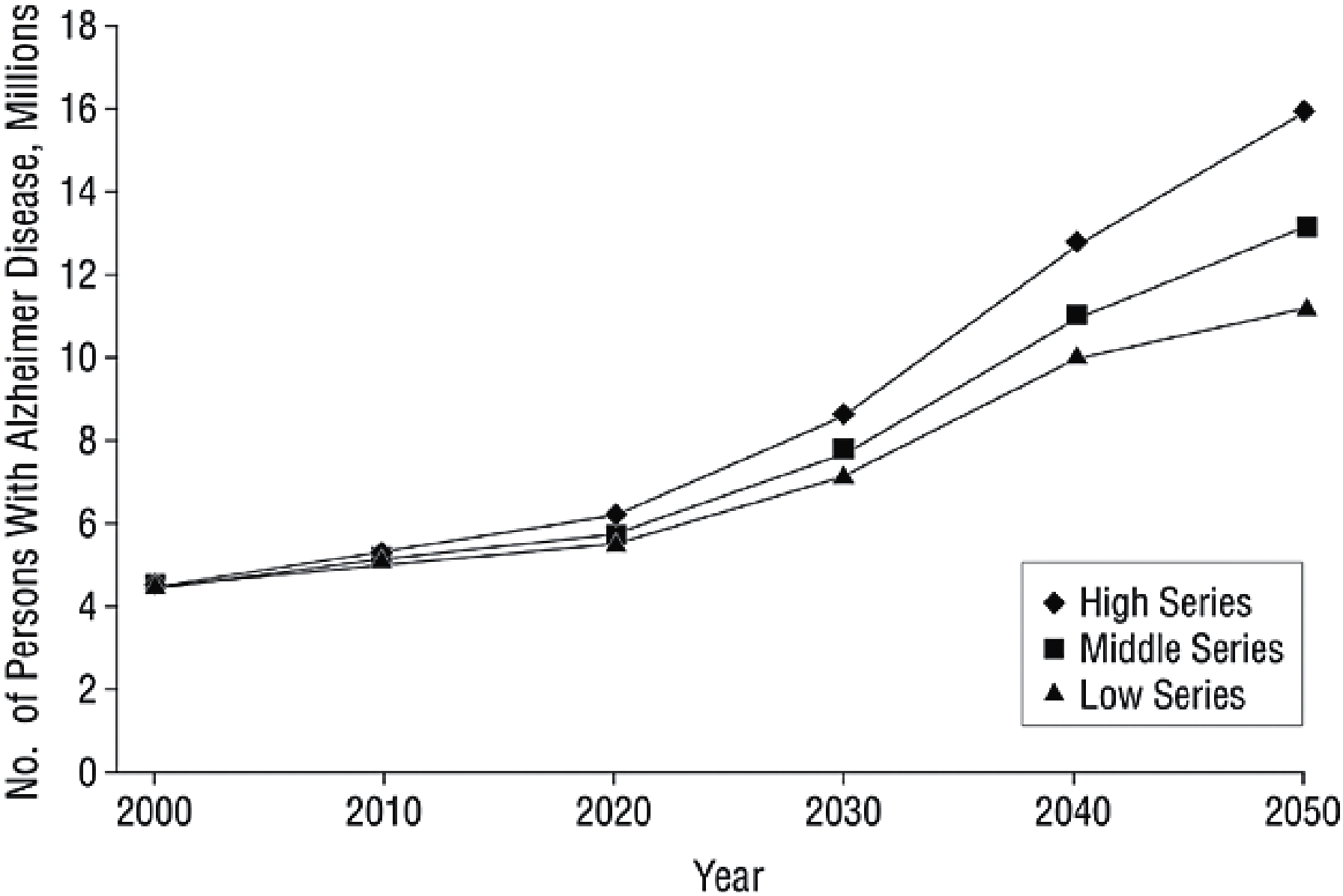
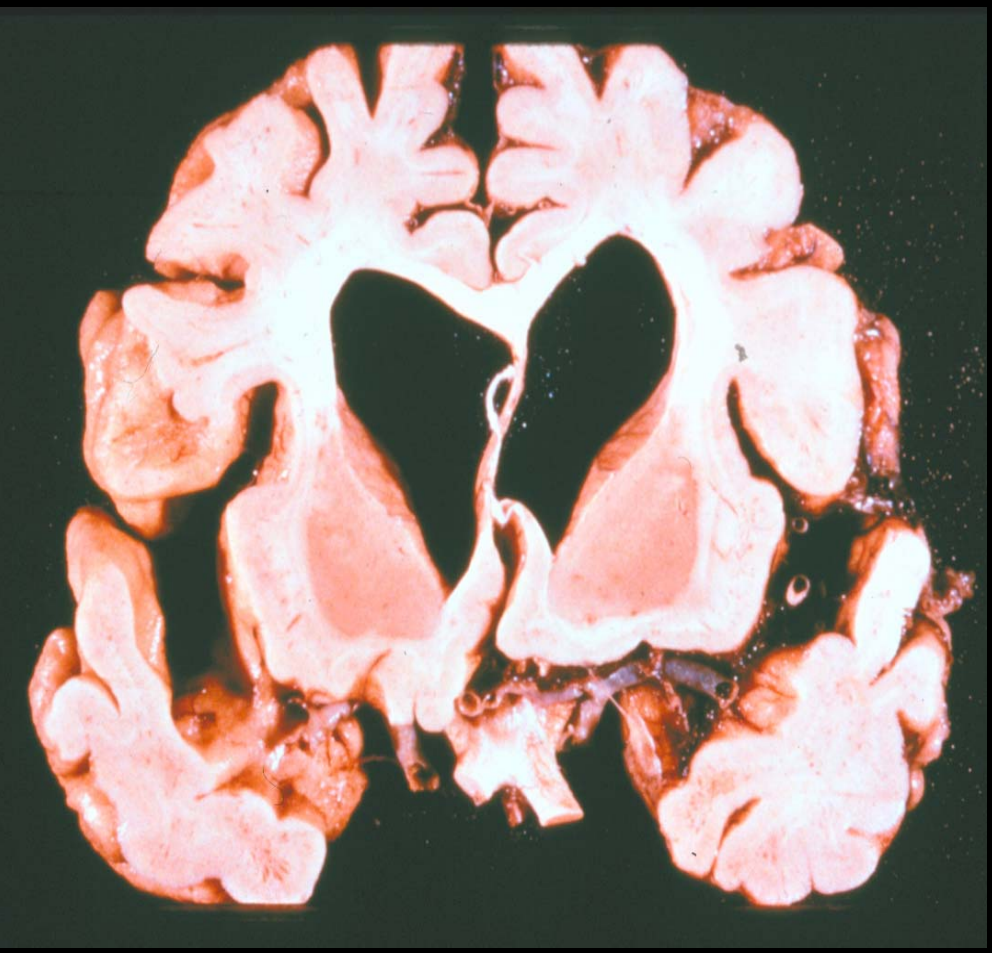

Number of Person in US over age 65
~37 Million
Number (000s)
90,000
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
2030
2040
2050
65-74
75-84
85+

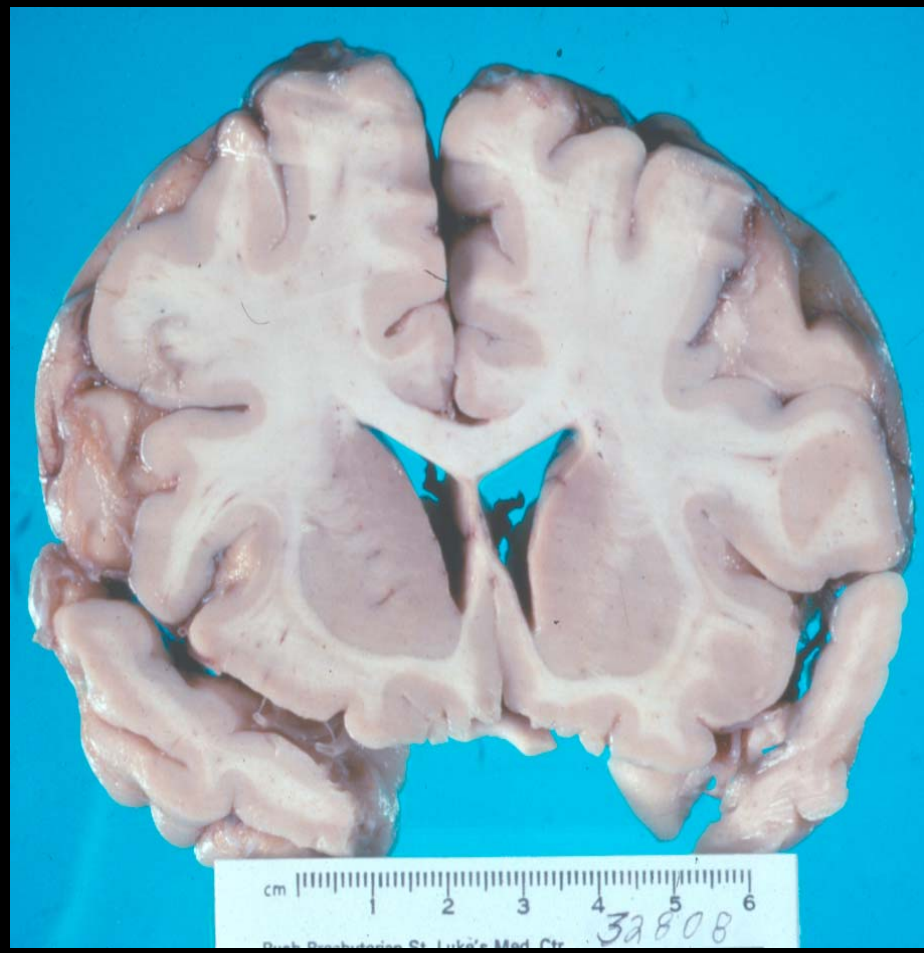
Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer's disease in the US population: Prevalence estimates using the 2000 census. *Archives of Neurology* 2003;60:1119-1122.



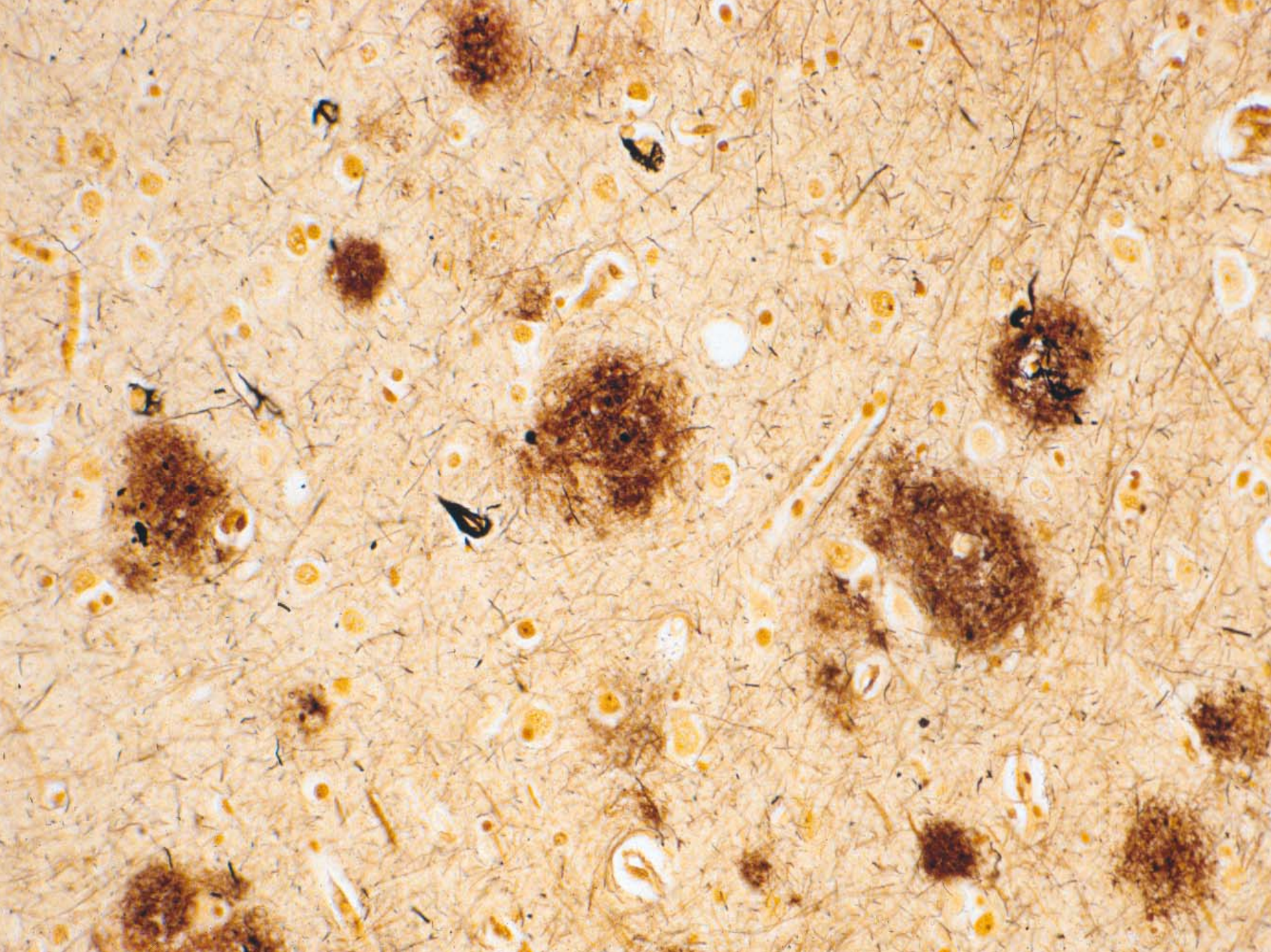
Alzheimer's Disease is an incurable, slowly progressive, degenerative brain disease that causes:

- Progressive loss of memory and other cognitive abilities
  - memory, language, attention, visuospatial ability
- Behavioral and affective disturbances
  - Psychotic symptoms, eg, hallucinations, misperceptions, delusions; agitation and aggression,
  - Depression
- Motoric
  - Parkinsonian signs, e.g., gait disturbance, and weight loss
- Caregiver distress and lost productivity
- Institutionalization
- Death

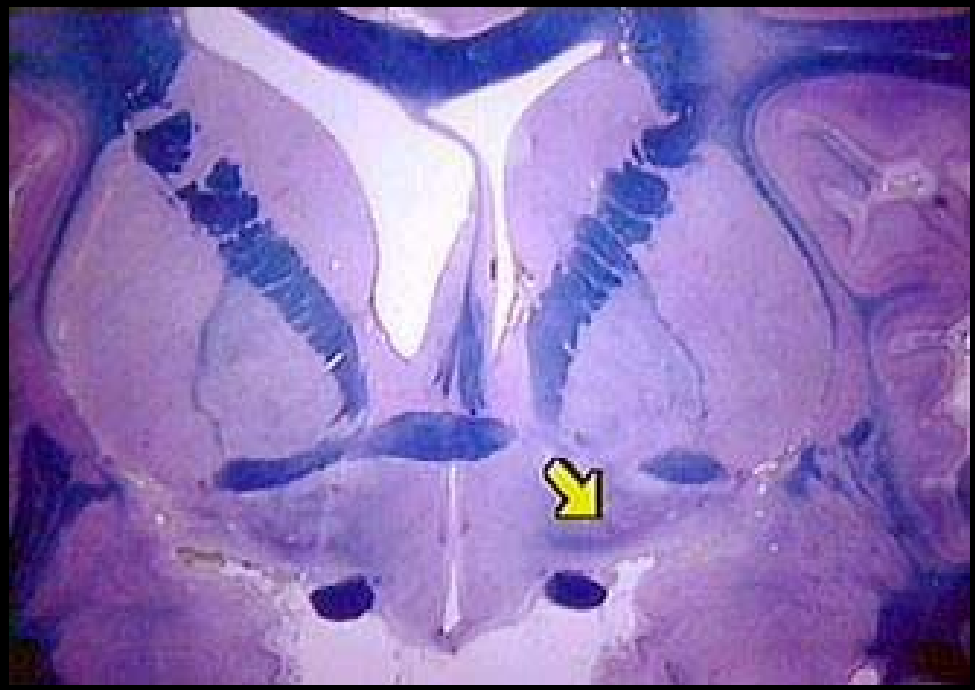


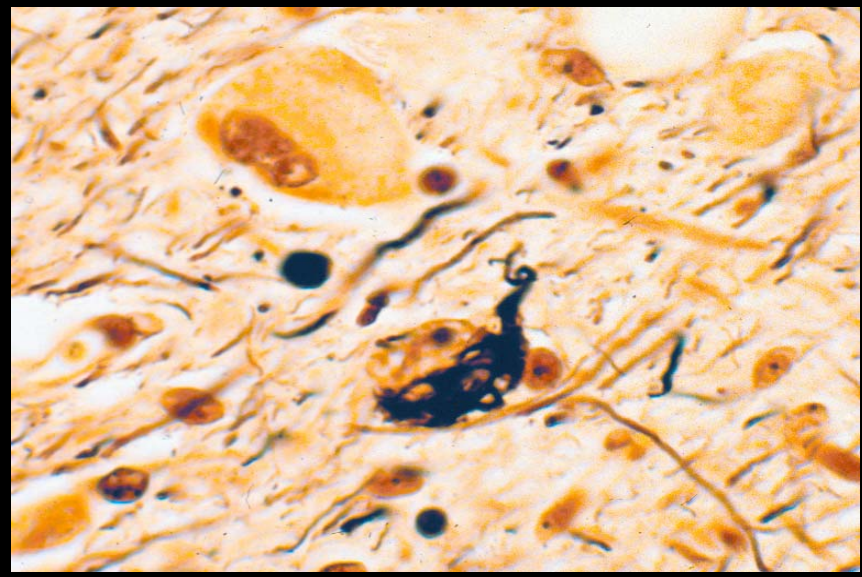


Bennett, DA; Rush University, CERE-110 for Alzheimer’s Disease; RAC; March 11, 2004



Cholinergic basal forebrain neurons (Nucleus basalis of Meynert)





-5 treatments approved by FDA
  - first 4 modulate this cholinergic system
- All symptomatic therapy
- None known to affect biology of disease

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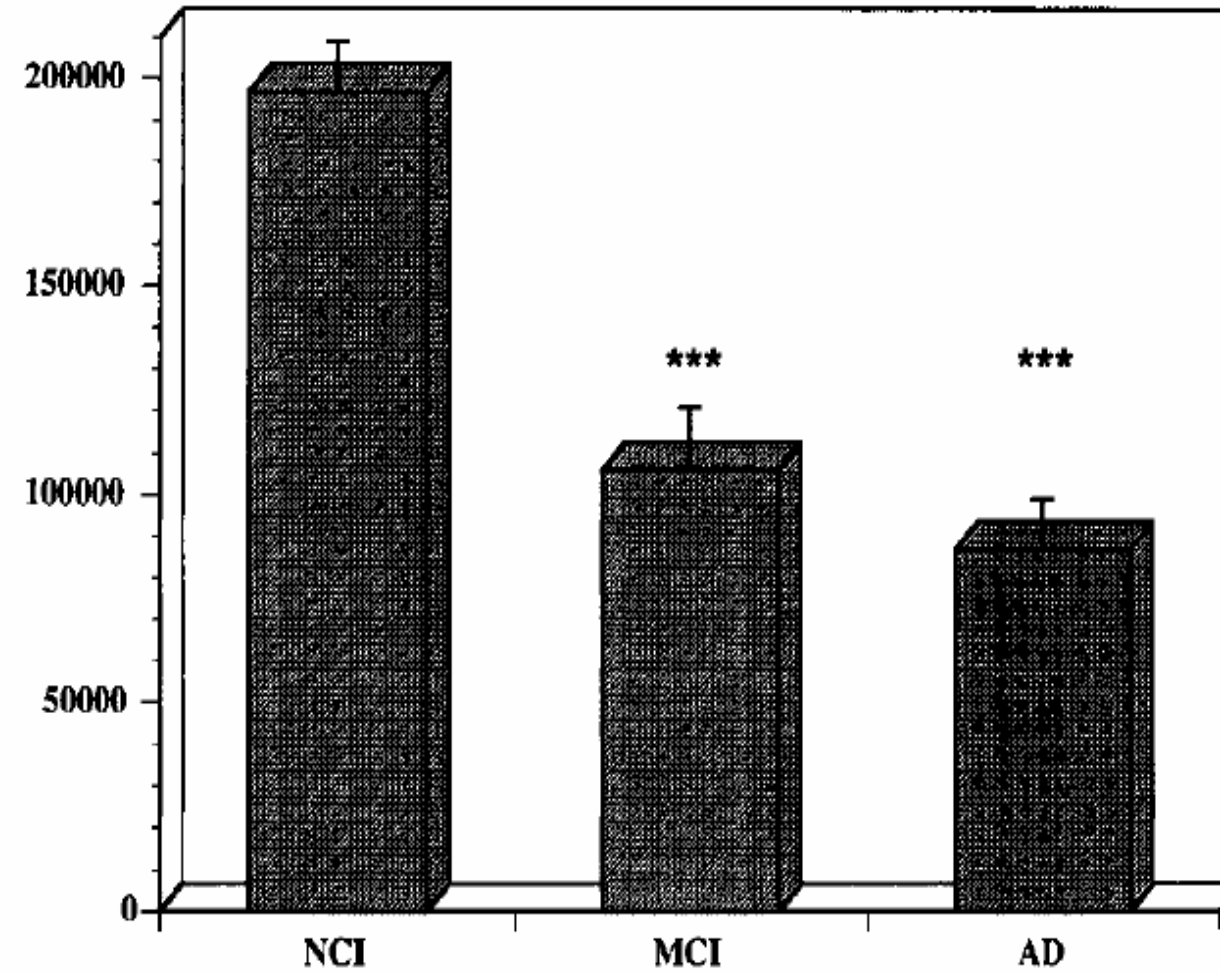
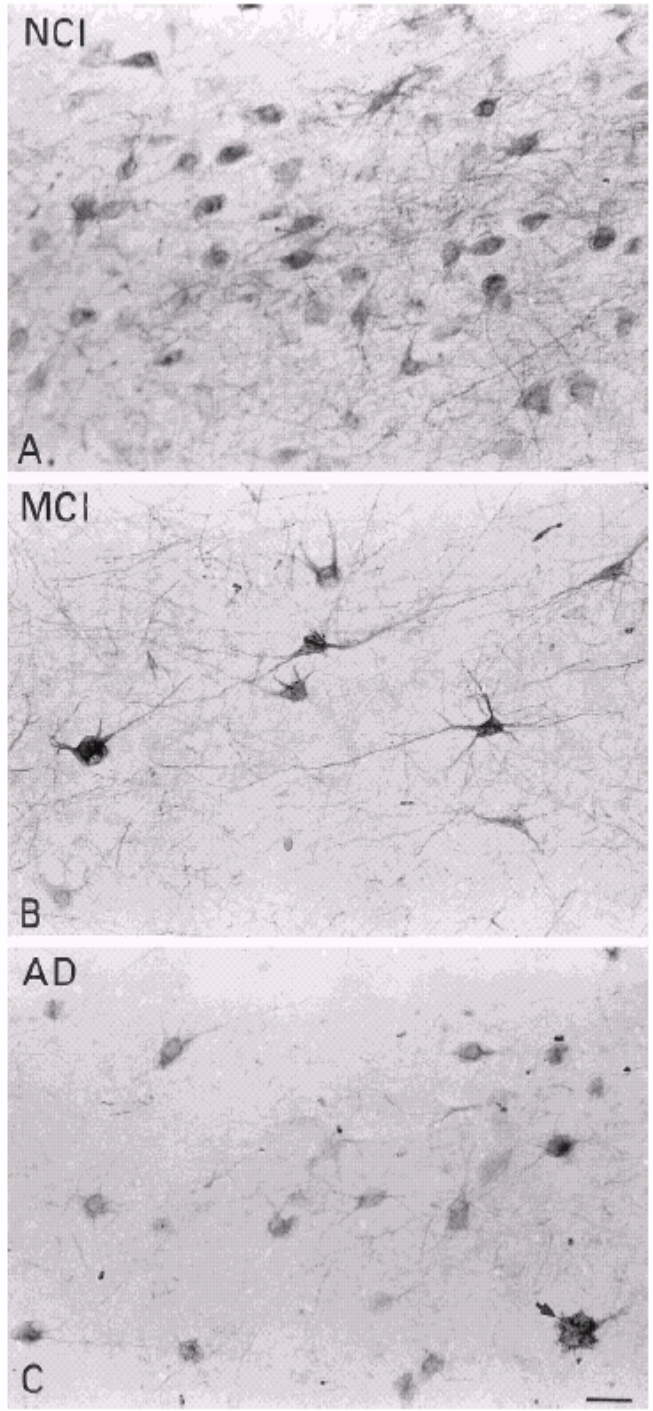
Mufson EJ, Ma SY, Cochran EJ, Bennett DA, Beckett LA, Jaffar S, Saragovi HU, Kordower JH. Loss of nucleus basalis neurons containing trkA immunoreactivity in individuals with mild cognitive impairment and early Alzheimer's disease. *Journal of Comparative Neurology* 2000;427:19-30.





CERE-110 for Alzheimer's Disease

A Phase I, Dose-Escalating Study to Assess the Safety, and Tolerability of CERE-110 (Adeno-Associated Virus (AAV)-based, Vector-Mediated Delivery of Beta-Nerve Growth Factor [NGF] in Subjects with Mild to Moderate Alzheimer's Disease.

Key Personnel, Rush University Medical Center

David A Bennett, MD – Principal Investigator (RADC)
Zoe Arvanitakis, MD – Co-Principal Investigator (RADC)
Jean Arzbaecher, MS, APN – Nurse Practitioner (CINN)
Roy Bakay, MD - Neurosurgeon (CINN)
Debra Fleischman, PhD – Neuropsychologist (RADC)
Danielle Mele, APN – Nurse Practitioner, Coordinator (RADC)
Gail Ruderman, RPh - Pharmacist

Phase I: Objectives

Primary

- To assess the safety and tolerability of two doses of CERE-110 administered stereotactically to subjects with mild to moderate Alzheimer's disease.
- To provide preliminary safety data from two doses of CERE-110 to support a Phase II clinical trial.

Phase I: Objectives

Secondary

- To determine the biodistribution of CERE-110 in serum and urine by PCR.
- To evaluate immunogenicity of the AAV vector and NGF by determining the antibody response to AAV and NGF.
- To obtain preliminary clinical outcome data, primarily to power further trials (e.g., ADAS-COG, ADCS-CGIC, CDR, MMSE, ADCS-ADL, Dementia Quality of Life-DQoL scales).

Two dose levels, 3-6 subjects each

- **First dose:** $8x10^9$ vector genomes 3 subjects
  - If no adverse events (grade 3, 4, or SAE), go to Second dose
    - If 1 adverse event, add up to 3 more subjects
    - If no additional adverse events, go to Second dose
- **Second dose:** $4x10^{10}$ vector genomes
- **A period of 1 month will transpire between the procedure on each subject.**
- Data on all participants will be collected, analyzed, reviewed by an independent Data and Safety Monitoring Board.

Methodology and Procedures

CERE-110 will be administered

- to the cholinergic neurons in the basal forebrain (Nucleus basalis of Meynert)
- using 4 injections (10 µL each); two on each side

- Study duration: 24 months. Subjects are asked to return for annual follow-up thereafter.

Inclusion Criteria

- Males or females (2 years postmenopausal), 50 to 80 years old.
- A diagnosis of Alzheimer's disease according to the (NINCDS/ADRDA) criteria.
- A score between 16 and 24 on the Mini-Mental State Examination [MMSE].
- On a stable dose of an acetylcholinesterase inhibitor for at least 6 months.

Inclusion Criteria (cont.)

- Good health with no clinically significant medical or psychological conditions.
- Informed Consent document signed by a competent and willing participant.
- In addition, an informed Consent document signed by;
  - a surrogate identified by the participant, or
  - a legally authorized power of attorney for Health Care, or
  - a family member identified according to the Illinois Health Care Surrogate Act.

Exclusion Criteria

- Any significant systemic illness that could put the subject at risk during the study or affect study compliance.
- Subjects who cannot undergo MRI or PET scanning (e.g., claustrophobia, metal implants, pacemaker).
- Subjects who have received any investigational agent or been exposed to investigational devices for 30 days prior to enrollment.
- Subjects with a history of receiving gene transfer products of any kind.