

U.S. House Committee on Foreign Affairs
Subcommittee on Africa, Global Health and Human Rights
Global Strategies to Combat the Devastating Health & Economic Impacts of Alzheimer's
Disease

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Good afternoon Chairman Smith, Ranking Member Payne and members of the Subcommittee. I appreciate very much being given the opportunity to testify before this committee on the global impact of Alzheimer's disease.

I am Hugh Hendrie, Professor of Psychiatry and Research Scientist at the Center for Aging Research at Indiana University and the original principal investigator for the Indianapolis-Ibadan Dementia project.

Studies that compare the rate of disease in one country to the rate in another country can help us understand the causes of the diseases. The value of these studies is greatly enhanced if they include comparisons from countries with very different environments such as those from the developed and developing worlds where the greater diversity of environmental exposure may make risk factors more identifiable. Alzheimer's disease is likely to be caused by a complicated interaction of genes, environment and toxic exposures. The recent explosion of knowledge about the genetics of Alzheimer's disease and the genetics of human populations now allows for the incorporation of both genetic and environmental information into these comparative studies. The promise of these studies would be to increase our understanding of Alzheimer's disease causation that is applicable to countries throughout the world and to identify risk factors in these countries that are modifiable. Currently there are few such international comparative projects exploring the risk for Alzheimer's disease and fewer still involving African nations. Currently about 70% of all the elderly worldwide are living in developing countries. The burden of caring for Alzheimer Disease patients in these countries is likely to be staggering.

The National Institute on Aging supported Indianapolis-Ibadan dementia project, which is now 20 years old, exemplifies this approach. The project is a longitudinal comparative study of the incidence and prevalence of dementia and Alzheimer's disease and their associated risk factors in 2 elderly community dwelling residents, African Americans residing in Indianapolis Indiana and Yoruba living in Ibadan Nigeria. Over 4000 residents in each community have been evaluated and followed over this period.

An outline of the evolution of the project and its major findings is included below and will be summarized in this brief presentation.

The Evolutionary Path of the Indianapolis-Ibadan Dementia Project

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INDIANAPOLIS—IBADAN COMPARATIVE EPIDEMIOLOGICAL
STUDY OF ALZHEIMER'S DISEASE

Supported by National Institute of Aging Grant AG09956
and
Alzheimer's Association/F.M. Kirby Foundation
Pilot Research Grant IRG-95-084

Goals of Comparative Epidemiological Studies

- Compare rates of illness between communities
- Analyze and compare risk factors for the illness
- Benefits of international studies- increase diversity

The First Venture – Dementia Screening Methods: Indian/Non-Indian Manitoba

*Supported by the
National Institute of Aging*

Hypothesis/Objectives for Indian/Non-Indian Study – The Influence of Culture

- Preliminary evidence suggested Alzheimer's Disease prevalence is low in Canadian Native Americans
- This pilot consisted of a comparative study between elderly Cree (treaty Indian) living on two reserves and non-Indian Winnipeg residents (pilot study)
- Eventual goal to conduct a survey of all elderly treaty Indians primarily Cree and Ojibwa living in Manitoba within and outside reserves

The Role of Ben Osuntokun in the Development of the African Project

The advantages of studying a migrant population

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Phase I – Epidemiology of Dementia/AD 1992 - 2001

- Objective
 - Comparative Study of Migrant Populations – African Americans and Nigerians with similar geographic origins now living in very different environments
 - Compare incidence rates of AD and dementia and their associated risk factors in Yoruba and African Americans
 - Risk Factors – Classical Epidemiological
 - Demographics
 - Medical Illness
 - Lifestyle Outcomes
 - Outcomes
 - Cognitive Decline
 - Cognitive Impairment not Dementia (multi-domain MCI)
 - Dementia
 - Alzheimer Disease
 - Mortality

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Phase I – Results

- AD was indeed present in Yoruba. Created major problems for the families but Dementia / AD Rates (Age-standardized overall rate – Dementia – African Americans 3.24 (2.11-4.38), Yoruba 1.35 (1.13-1.56); AD – African Americans 2.52 (1.40-3.64), Yoruba 1.15 (0.96-1.35) – Lower in Yoruba (but both rates were within the published limits for international studies. No comparative studies in Africa)
- Vascular Risk Frequency * (BMI, Cholesterol levels, Hypertension, Diabetes) – Lower in Yoruba
- Lifestyles Differ by Population

Risk Factors	African Americans	Yoruba
	↑	
Increasing Age	↑	↑
Gender (female)	ns	↑
Low Education	↑	ns
Low Education / Rural Residence	↑	ns
High Social Involvement	↓	↓
Medication		
• Anti-hypertensive	↓	ns

NOTE: ns = not significant, ns = not significant
 ↑ Increased Risk ↓ Protection

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The Genetic Explosion

- Background
 - Population Genetics – Out of Africa
 - Modern humans originated in Africa and spread throughout the world in a series of migratory waves
 - Risk alleles for chronic illnesses distributed throughout the world across populations are likely to have originated in Africa
 - Studies of genetic risk in AD
 - APOE ε4 is a major risk factor for AD in most populations.

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Phase II – Explore Mechanisms of Dementia/AD - 2001

• Objective / Hypothesis

To build upon our initial findings and intensify our exploration of potential risk factors for dementia/AD by:

- Adding biomarker measurements from blood samples to assess cardiovascular risk and recording vital signs including BP at all visits
- Expanding the genetic studies to include DNA from all consenting participants and analyzing APOE and related genes
- More sophisticated lifestyle assessment
- Enrich population

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Modeling the Contribution of Genes & Environment

Observed Phenotypic Variation = Genes + Environment +

Genes * Environment + Genes * Genes + Environment * Environment

Models for the nature-nurture construct

Cooper and Kaulman, 1998

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Biomarker Means and Standard Deviations

	Indianapolis (n=1516)	Ibadan (n=1254)	
	Mean ± SD	Mean ± SD	P-value
Cholesterol (mg/dL)	186.66 ± 40.11	174.61 ± 40.88	<.0001
HDL (mg/dL)	51.23 ± 15.59	50.02 ± 13.79	0.0307
LDL (mg/dL)	112.75 ± 34.51	106.70 ± 33.30	<.0001
Triglycerides (mg/dL)	113.40 ± 55.58	89.47 ± 36.44	<.0001

In 2001 22.3% in Indianapolis on statins
NB Ibadan had higher levels of a measure of oxidative stress

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Phase II – Results

Risk Factors	African Americans	Yoruba
APOE ε4	↑ (Aβ, Mortality)	Marginal
Diabetes	↑	ne
Hypertension	ns	↑
High Social Engagement	↓	↓
Hemoglobin levels	↑	↑
Lipids * APOB	↑	↑
Medication		
Antidiabetics	↑	ne
Statins	↓?	ne

Notes: ns = not significant; ne = not evaluated

↑ = increased risk ↓ = protective

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Implications for Site Differences in APOEε4 Effects and Alzheimer's Disease Risk

- Genes other than APOE ε4 increase risk
 - Gene clusters that may protect against APOE ε4 effect
- Environmental factors may result in alterations in gene function

Expansion of Genetic Studies

African Americans

- Alzheimer Disease Genetic Consortium
- Genome-Wide Association Study of Cognitive Decline among older African Americans

Nigerians

- Genome wide association of cognitive decline in Nigerians (nb) - this will be the largest available sample of well characterized elderly people in Africa

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