Cross-cultural Studies and the Search for Risk Factors in Alzheimer's Disease

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Introduction

It is a great honour and privilege for me to be invited to give this lecture in memory of a man who was not only a respected colleague, but a very close and personal friend. His untimely death was a great blow to me and to my family, both personally and professionally.

It would be superfluous of me to recount the extraordinary life and accomplishments of Professor Osuntokun. These are well known to this audience and have been aptly described in scientific journals and distinguished newspapers by other authors throughout the world. Suffice it to say that some years ago, when the International Psychogeriatric Association asked me to recommend a distinguished African physician who could serve on their board and be the keynote speaker at their biannual symposium, I did not hesitate to recommend Professor Osuntokun. He was truly a remarkable man and a towering figure in the world health community, a man who excelled in all aspects of life. Upon re-reading the eulogies written after his death, I was struck again by the obvious intensity of feelings that Ben had generated within the various authors, illustrating perhaps his most unusual confluence of qualities. Ben did not only possess a first class intellect, it was his personal qualities of enthusiasm, warmth, charm, empathy and understanding which made knowing him so special.

My introduction to Ben came through our mutual interest in epidemiological studies. When Dr. Kathleen Hall and I were preparing for our first foray into cross-cultural research — involving the Canadian Cree Indians — and reviewing the

existing literature, we were struck by the creativity and clarity of the accounts of Ben's research with the late distinguished Bruce Schoenberg in Copiah Country and with his colleagues studying neurological disorders in Nigeria. We were determined at that time to engage him in some way as a colleague, and corresponded with him on several occasions. My first opportunity to meet Ben was at a WHO-sponsored meeting in Zaragora Spain, where both the audience and I were spellbound, not only by his erudition, but also by his obvious deep and abiding love for, and commitment to, Nigeria. In Dr. Osuntokun, Nigeria had one of its finest ambassadors. My wife and two of my children attended that meeting with me and there began the friendship, not just between us, but between our families.

Shortly after that, we were able to obtain funding from the National Institute on Aging. The funding allowed Ben to spend a year's sabbatical with us in Indianapolis while we were undertaking the Cree study. It was during this year that we also devised and wrote the application for the Indianapolis-Ibadan study. Some of my fondest memories of him were when he accompanied us on our visits to the subarctic reserves of the Cree, braving 40 below zero weather to conduct clinical assessments. It was then I began to realize what a superb clinical neurologist he was. Ben was painstaking, meticulous, and persevering, — as are all good neurologists — yet very sensitive to the concerns and needs of his patients. He was very much a hands-on research scientist, the analysis of data collected by another was not for him. Up until his death, Ben was conducting clinical assessments of our subjects in the Idikan wards. During his sojourn in Indianapolis, I was also greatly impressed with Ben's work ethic and his continual search for knowledge. When

he was not working with us, he would spend endless hours in the library.

It was not all work, however. Ben was accompanied by his wife, the equally talented and charming Olabopo and together we had many pleasant evenings, which Marguerite and I remember very fondly.

It was during this year, 1989, that the Indianapolis-Ibadan study was conceived, and the successful grant written. We have been fortunate in this study to have access to outstanding faculty and staff, both at the University of Ibadan and the University of Indiana. We have been blessed with access to superb consultants from the United States and from Europe, but I believe, it is fair to say that without Ben's creativity, influence and persistence, this project would simply not have occurred. It is particularly sad, therefore, that now when we are beginning to enjoy the fruits of our endeavours and beginning to present and publish what we believe to be exciting findings, Ben is not with us to share in these presentations. I believe Ben would have been proud of the high esteem in which this study is now held. In our last grant submission, the study section wrote, 'Enthusiasm is high for this important, difficult, and in many ways ground-breaking study, which has made excellent progress under challenging circumstances and has produced intriguing preliminary data.' Our study has also been cited as an example of cross-cultural research in a number of previous articles, including one by Prince et al.

One of Ben's outstanding attributes, was his ability to transmit his enthusiasm and erudition to his students. As a result of this, we are able to continue our study through the efforts of his younger colleagues, Drs. Ogunniyi, Baiyewu, Gureje, and others. Nevertheless, Ben is sorely missed.

For the remainder of my presentation, I would like to discuss the rationale for cross-cultural studies, describe some of the studies currently taking place and finally, review the progress of our Indianapolis-Ibadan project.

The Value of Cross-cultural/Transnational Research

Descriptive Studies

Dementing disorders affect approximately 5 to 11 per cent of the community-dwelling population aged 65 years and over in Western societies, with the prevalence rates approximately doubling every five years after age 65 and rising to more than 30 per cent in patients 85 years of age and over. If milder forms of dementing disorders are included, an additional 10 per cent or more of the elderly population may be affected. Approximately half or more of all nursing home residents have dementia. In most studies, Alzheimer's Disease (AD) accounts for approximately two-thirds of all cases of dementia. It has been estimated that the cost of managing dementia in the United States in 1991 was $67 billion. The direct expenditures in the United Kingdom have been estimated at £738 million. These costs ignore the enormous social and economic impact on care givers. Dementia, therefore, represents a major public health problem to Western society and one that is only likely to increase over the next several decades, given the current demographic trends. The study of dementing disorders has not received adequate attention in developing countries, where it has been regarded as a relatively uncommon condition, with few persons surviving into the age group most at risk. Nevertheless, over half of the elderly people worldwide live in developing countries and by the year 2025, this percentage will probably increase to over 70 per cent. If the prevalence rates of dementia in developing countries in any way parallel the rates of dementia in developed countries, then

about three quarters of all cases of dementia would be in these countries.

So far, in most developing countries, control of communicable and deficiency diseases has been the major priority. Due to increasing life expectancy, there is an ongoing epidemiological transition, and diseases of the elderly such a cancer and dementia have emerged as major public health problems. One vital aspect of cross-national research, therefore, is to provide data to enable public health professionals in the developing countries to determine and allocate health resources to meet these needs.

Risk Factors in Alzheimer's Disease

In addition to age, gender, and family history, increased risk of developing AD has been associated with a low level of education, previous head injury, depression, hypothyroidism, diabetes and exposure to certain chemicals such as pesticides, industrial pollutants, aluminium and zinc. Reputed protective effects against the development of AD have been proposed for antioxidants, (particularly vitamin E), non-steroidal anti-inflammatory drugs (NSAIDS), and estrogen replacement therapy for post-menopausal women. Risk factor research has, however, been plagued with inconsistent and non-replicable results, in part due to wide variations in the methodologies used in these studies. In 1992, Professor Osuntokun wrote, 'Comparative cross-cultural, transnational, geographic epidemiological studies would be useful to delineate the true risk factors of the age-associated dementias, particularly AD.' Identification of populations or communities with significantly lower or higher prevalence rates of AD could greatly enhance the search for environmental risk factors of AD, as we could then compare cultural factors and relative exposure to putative disease pathogens or

environmentally produced noxious agents. The chances of delineating environmental factors and separating them from genetic factors are increased if the same ethnic group, at different levels of development and in different environments, but with true differences in the epidemiology of the disease, is available for investigation. It is also possible that such studies would identify as a risk factor of AD exposure to some environmental elements to which humans are not adapted, and which are ubiquitous in Western societies, but not present in non-industrialized countries.

Professor Osuntokun warned, however, that these studies need to be conducted quickly because of the rapid transformations occurring in non-industrialized countries, which are continually eroding the traditional lifestyle of these populations and making these populations more exposed to both the advantages and disadvantages of westernized society.

Genetic Risk Factors

The revolution in molecular genetics has transformed our understanding of the aetiology of AD. There is now evidence that certain types of familial, autosomally dominant AD are associated with mutations on a gene locus on chromosome 21, encoding for the amyloid precursor protein; and mutations on gene loci on chromosomes 14 and 1, encoding for the so-called presenilin proteins. These findings are extremely important for the development and understanding of the pathophysiological mechanisms of AD, but account for only a very small proportion of all Alzheimer cases (perhaps about 2 per cent). Recently, some forms of late onset AD have been linked to a yet unidentified gene on chromosome 12 (table 1).

Table 1. Gene mutations and associations in AD

Gene	Chromosome Location	Gene Product	AD Association
APOE	Chromosome 19q13.2	Apolipoprotein E-ε4	Late-onset familial and sporadic AD
APP	Chromosome 21q21	β-amyloid precursor protein	Early-onset familial AD
PS 1	Chromosome 14q24.3	Presenilin-1 (protein $S18_2$)	Early-onset familial AD
PS 2	Chromosome 1q31.42	Presenilin-2 (protein STM2)	Early-onset familial AD
?	Chromosome 12	?	Late-onset familial AD

A Sahota and HC Hendrie, 1997

Apolipoprotein E (*APO*E) is a serum lipoprotein involved in cholesterol transport. Its three common isoforms are encoded by alleles 2, 3, and 4 on chromosome 19. Considerable excitement has been generated by the recent finding of an association between the ε4 allele of *APO*E and AD. This association has been reported for the most common forms of late onset AD, both sporadic and familial. The association is dose dependent. Individuals who are homozygous for the ε4 allele (i.e., possess two copies) are at a greater risk of developing AD than individuals who are heterozygous (i.e., possess one copy). In earlier studies, it was reported that subjects who possessed a single copy of the ε4 allele, were 4 times more likely to develop AD, and subjects who possessed a double copy of the ε4 allele, were 8 times more likely to develop AD. Case control studies have suggested that the association between *APO*E-ε4 and AD may account for 30-40 per cent or more of all cases of AD.

Population-based studies, however, while still showing significant associations, have reported lower risk ratios (about 2 for single copies of the ε4 allele) and lower estimates of the proportion of cases of AD accounted for by this association (10-20 per cent). A few studies have suggested that the *APO*E-ε2 allele may confer a protective effect against AD, but this has not been consistently observed in all studies. There now appears to be increasing evidence that the association between *APO*E-ε4 and AD is both age and gender related. The strongest effects of this association occur between the ages of about 50-75 years of age and tend to become weaker in the oldest age group. Women who possess the *APO*E-ε4 allele appear to be at a higher risk of developing AD than men who possess the ε4 allele.

The association between *APO*E-ε4 and AD has been confirmed in many studies in Caucasian and Japanese populations. It is however too early to determine whether or not the relationship will be similar in all population groups. This will be discussed in more detail later on in this paper. Variations in risk association between genetic factors and illness across ethnic groups is not an uncommon phenomenon. It has, for example, been reported for molecular variants of the angiotensinogen gene in populations of African origin. This reinforces the concept that a full understanding of the genetic contribution to the pathophysiology of illness requires the evaluation of several different ethnic groups.

Indeed one intriguing feature of the studies conducted so far on *APO*E, is the marked variation in frequency of the ε4 allele found in different populations and ethnic groups. Reported frequencies of ε4 have varied widely between populations, ranging from 5 per cent or less in the Amish populations to over 40 per cent in some aboriginal populations (see table 2). It is not

clear yet what effect these population frequency variations have on the association between *APOE* ε4 and AD.

Table 2. ε4 allele frequency in populations

Population	ε4 Allele Frequency (%)
Amish	3-5
Japanese	8
Caucasian	11-16
Finnish	24
African-American	23-25
Some Aboriginal populations	40-50

HC Hendrie, 1998

Our ability to identify risk factors at the genetic level also has significant implications for epidemiological research. It is no longer necessary to consider, at the risk factor level, vague, ambiguous at best, and politically-charged concepts such as race or ethnicity. A recent editorial in Science was entitled, 'DNA Studies Challenge the Meaning of Race.' Sophisticated aetiological hypotheses involving specific genes and specific environmental factors can now be formulated to explain geographic or ethnic variations in disease rates.

This development has recently been applauded by Cooper and Kaufman. They state: 'Collectively we should abjure the use of race as an indicator of intrinsic risk in aetiologic studies; a paradigm which is destructive to the scientific search for truth and which by casting social reality as biological reality, perpetuates racism and harms society at large.' These remarks

are probably particularly pertinent to the still racially-polarized society in the United States. Unfortunately, it is not certain to me, given the discriminatory propensity of humans, whether or not molecular understanding will entirely eliminate the risk of racism.

Another off-shoot of the study of population genetics is of interest to this audience. Kidd and his associates have studied a wide variety of polymorphic loci to investigate the extent of human genetic diversity and to delineate the relationships between modern human populations. These analyses have tended to support the anthropological hypotheses regarding the African origin of modern humans.

> Overall, and taken together with the results of other studies, our data is most consistent with a third [sic] explanation that there has been a major diversion in the origin of modern humans between African and non-African populations with a founder non-African population arising from a subset of a larger population found in Africa.

Consistent with this hypothesis, Kidd has demonstrated that there is a higher genetic diversity amongst Africans than amongst non-Africans. This is also seen in the frequencies of ε4 within African populations where the variation is at least as great as the worldwide variation presented in table 2.

Proposed Disease Model

I am not suggesting that there are differences between the pathophysiological processes underlying AD in Africans, African Americans or Caucasians. Neither am I suggesting that the fundamental biological effect of any single risk factor, genetic or

environmental, differs between the populations. Rather, it is the additive effects of the presence or absence of these individual factors, genetic or environmental, or the interaction between these factors which would account for different rates of AD between the communities. Based upon a proposal by Cooper and Kaufman, this model for AD would be as follows:

Occurrence of AD in the populations =
Genes + Environment +
Gene/Environment Interaction +
Gene/Gene Interaction +
Environment/Environment Interaction.

Our studies of two communities from very different environments will allow us, hopefully, to identify these interactions.

Cross-national Studies

There are two other major comparative international epidemiological studies of AD involving either developing countries or migrant populations in addition to our Indianapolis-Ibadan Study. They are the Indo-US Cross National Dementia Epidemiology Study and the Ni-Hon-Sea Project Studies (table 3).

Indo-US Cross-National Dementia Epidemiology Study

The Indo-US Cross National Dementia Epidemiology Study is a comparative study of the epidemiology of the dementing disorders in an elderly population in a rural district of northern India, and a population of elderly subjects living in the Monongahela Valley in Pennsylvania USA (MoVIES Project).

Table 3. Age standardized prevalence rates of dementia in comparative international studies (Canadian study as reference)

Studies	Criteria	Age (years)	Rates (%)	Pre-dominant subtypes
Ni-Hon-Sea				
Japanese American (Seattle)	DSM-III-R	65+	6.3	AD
Japanese American (Honolulu)	DSM-III-R	Over 70 (men only)	7.6	AD
*Japanese (Hiroshima)	DSM-III-R	60+	5.3	AD (in women)
Indianapolis-Ibadan				
African Americans (Indianapolis)	ICD-10	65+	8.24	AD
Yoruba (Ibadan)	ICD-10	65+	2.29	AD
Rural India				
Hindi Speaking	DSM-IV	65+	1.36	AD
Canadian				
Cross-national (English Speaking)	DSM-III-R/ICD-10	65+	8	AD

*Abstract only available.

N.B. No prevalence rates as yet are available from the Indo-US Study.

The investigators have reported an overall prevalence rate of 1.36 per cent (0.96-1.88; 95 per cent confidence limits), for dementia and of 0.62 per cent (0.43-0.88; 95 per cent confidence limits), for AD for the Indian population of 65 and over. These rates are much lower than those reported for the residents of the Monongahela Valley and similar to but even lower than the rates reported from Ibadan. The authors are cautious about the interpretation of these differences suggesting they may be due to differences in overall life expectancy or shorter survival rates for subjects with the disease in India. They also speculate that if the differing prevalence rates represent real differences in disease

rates, it may be due to differences in the underlying distribution of risk and protective factors in the Hindi population in comparison to populations in Western countries.

The Ni-Hon-Sea Project

The Ni-Hon-Sea Project consists of a group of independently-funded comparative studies of dementia and aging in sample Japanese populations at three different sites: Hiroshima, Japan; Kings County, Washington (The KAME Project); and Oahu, Hawaii. The Hawaiian study is part of the Honolulu Heart Programme. These studies, while all independent of each other, have used comparative methodologies, screening and clinical instruments. Prevalence rates of dementia and AD in the Hawaii and Washington sites have been published, and preliminary prevalence rates have been reported from Hiroshima. Both groups of investigators of Japanese-American populations in Seattle and Honolulu, have commented on the similarity of their reported rates of dementia, and their finding that AD is the predominant dementia subtype in Caucasian populations in North America and Europe, suggesting a strong environmental influence on disease rates. They also commented on the differences between their studies and previously reported studies of dementia in Japan where vascular dementia predominates. In the preliminary results from the Hiroshima study, however, AD was the predominant dementia subtype in women, but in men, the rates of AD and vascular dementia (VD) were more or less equal.

An intriguing preliminary finding of the Seattle-based Japanese-American study, was that the preservation of the Japanese lifestyle in subjects was associated with the low levels of cognitive decline and lower rates of AD in those subjects.

The Indianapolis-Ibadan Study

The Indianapolis-Ibadan Study was conceived and designed during Professor Osuntokun's sabbatical in Indianapolis. It was proposed partly because of the aforementioned potential advantages in studying a migrant population at various stages of social and economic development, and also because of the results of previous epidemiological and autopsy studies which Professor Osuntokun had conducted in Ibadan. These included a 1987 community-based study of neurological disorders involving over 19000 subjects, a study of 2182 consecutive new patients seen at the neuropsychiatric hospital at Aro, and an autopsy survey carried out on the brains of 198 Nigerians who died at age 40 years or over, including 65 from individuals older than 65 years. In all these studies there was neither clinical nor neuropathological evidence of AD in any of the subjects. Professor Osuntokun concluded, therefore, that AD, if it occurred at all amongst Nigerians was rare. On the other hand, from our clinical experience in Indianapolis, AD appeared to be as common in African Americans as in Caucasians. Our hypothesis, therefore, was that the rates of AD would be significantly lower in the Yoruba than in the African Americans and that the reasons for these rate differences would be found in the differential distribution of environmental risk and protective factors. It must be remembered that these deliberations took place prior to the explosion in genetic knowledge of the disorder. The project has been continuously funded by grants from the National Institute on Aging and the Alzheimer's Association since 1991. The timeline for our studies is shown in figure 1. We are currently just completing our second incidence wave, four years after our initial prevalence study.

One of the first tasks we faced was to overcome the many major methodological problems involved in cross-cultural

research, particularly when the research involves — as ours did — populations which are partly illiterate. Three major issues were the construction of a sampling frame, development of culture fair instruments and comparability of diagnoses across sites.

In industrialized countries when accurate census data is available, attempts are usually made to derive a representative sample of that population using the data. In countries where there is a lack of census data, however, and particularly when rates of the illness studied are likely to be low, a total population survey of a geographically defined area is desirable. As pointed out in the World Health Organization (WHO) protocol for Research on Aging sampling, an entire village or well-defined area offers the advantage of clear structural homogeneity and decreases the likelihood of missing cases of dementia. The latter technique, however, has the disadvantage of lack of generalizability. In our Indianapolis-Ibadan study, both

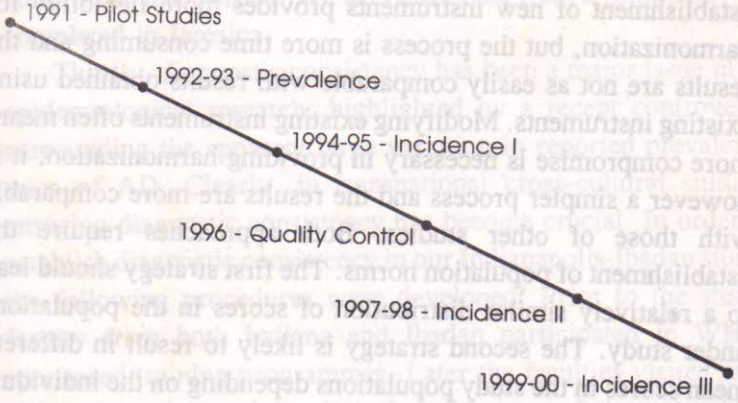

Figure 1. Idianapolis-Ibadan longitudinal comparative epidemilogical study of Alzheimer's Disease

techniques were used. In Indianapolis, a representative sample of African Americans was constructed using census data and in Ibadan a total sample of an area of the city of Ibadan (the Idikan wards) was chosen.

The second major challenge of cross-cultural studies in dementia is the development of culture fair instruments for assessment. Two basic approaches have been employed. One approach is to develop new instruments based upon the domains of the syndrome of dementia to be measured; viz, memory, language, judgement, etc. The other approach is to start with already existing instruments and to modify them so that they can be used in the different cultural settings. There is considerable overlap between these two approaches and both have processes in common, such as translation, back translation and most importantly, harmonization. 'Harmonization' means that the instrument must be harmonious or consistent with the cultural, linguistic and educational norms of the subject population. There are advantages and disadvantages to both approaches. The establishment of new instruments provides more flexibility for harmonization, but the process is more time consuming and the results are not as easily comparable with results obtained using existing instruments. Modifying existing instruments often means more compromise is necessary in providing harmonization; it is however a simpler process and the results are more comparable with those of other studies. Both approaches require the establishment of population norms. The first strategy should lead to a relatively similar distribution of scores in the populations under study. The second strategy is likely to result in different mean scores in the study populations depending on the individual test characteristics.

In our Indianapolis-Ibadan study, we constructed a relatively new screening instrument designed originally for our Cree study

which included both cognitive testing and informant data about performance in every day living the Community Screening Instrument for Dementia (the CSI'D'). This instrument has now been used with comparable results and with good sensitivity and specificity in Caucasian, Cree, and Chinese, as well as our African-American and Yoruba populations. The complicated steps necessary to construct this instrument have been described elsewhere. They include identification of the dementia domains, selection and translation of items from these domains with indigenous investigators, preparation of first drafts for the test of acceptability, reviewing, pretesting and pilot-testing second drafts, and revision of these drafts based upon statistical analysis for use in the major study.

For our clinical evaluation, we decided to use primarily the existing Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery which again was translated, back translated and harmonized. We now have available normative data from the CERAD subtests on African-Americans and Yoruba. We also have data from a pilot study we completed in Jamaica.

Thirdly, diagnostic consistency has been a major issue in all epidemiological research, highlighted by a recent controversy surrounding the apparent large variation in reported prevalence rates of AD. Clearly, in transnational cross-cultural studies, ensuring diagnostic consistency has become crucial. In order to establish diagnostic consistency in our Indianapolis-Ibadan study, the following procedures were developed. Prior to the study, faculty from both Indiana and Ibadan participated in WHO-sponsored training programmes. Later the faculties visited each site and participated in clinical evaluations of dementia. The diagnostic process was as follows: comprehensive, neuropsychological, informant, neurological, physical and where

necessary laboratory data, were collected. All subjects were seen by a physician/investigator. A consensus diagnostic conference was then conducted at each site where the health care personnel — including the examining physician the neuropsychologist and at least one other senior investigator — reviewed all the data and arrived at a preliminary diagnosis. Physicians from Indianapolis and Ibadan then made exchange visits to review the clinical data, visit selected subjects and, blind to the preliminary diagnosis, make independent diagnoses. A final consensus conference involving faculty from both sites resolved differences between sites and arrived at the final diagnosis. This type of consensus diagnosis depends obviously on having a group of well-trained physicians at each site. One pleasant outcome of the frequent exchange visits by the two faculties is the close friendship — both personal and professional — that has developed.

Another major problem in all community-based studies is ensuring the cooperation of the study population. The Idikan wards were selected by Professor Osuntokun because of his experience with this population in prior epidemiological studies. Professor Osuntokun continually insisted that in order to ensure cooperation it is necessary to provide services to the community in return. With this in mind, as part of the budget contract with the University of Ibadan, Professor Osuntokun provided for at least, a minimal amount of health care for the participants in the study in addition to a small stipend. He also made certain that he met periodically with the community elders (one of which I attended with him) to inform them about the study and respond to their requests. As a result of his efforts, refusal rates from subjects in the Idikan wards were very low (1-2 per cent).

The situation in Indianapolis was potentially even more difficult. The African-American community in the United States is justifiably very suspicious of the medical and research

establishment after the notorious Tuskegee incident, and refusal rates for studies such as ours are usually very high — close to 50 per cent or above in some studies. Dr. Hall devoted most of her time during the first year trying to ensure community cooperation. This involved selecting an external advisory board consisting of community leaders, and meeting with these community leaders individually and collectively. Church and religion play a very significant role in the lives of the African-American community. Thus, a great deal of time was devoted to meeting with the members of the various churches, describing our study and its potential benefits to their congregations. A number of articles were also placed in the local African-American newspapers and on the radio. Finally, a group of highly skilled African-American interviewers, who were familiar with and familiar to the community subjects, were selected. As a result of all these efforts, the refusal rate in Indianapolis was also very low (less than 11%).

The results of our prevalence studies were published in 1995. We reported significant differences in the age-adjusted prevalence rates of dementia for ages 65 years and over (8.24 per cent in Indianapolis, 2.29 per cent in Ibadan), and of AD (6.24 per cent in Indianapolis 1.41 per cent in Ibadan) (see tables 4a and 4b). It should be noted that although the rates were consistently lower in Ibadan, the association of disease with age was identical in both sites; i.e., prevalence rates in both sites roughly doubled every five years. This leaves open the possibility that the combination of genetic and environmental effects in Idikan, which results in the lower rates, does so by delaying the onset of AD in Ibadan, by about 5 to 6 years in comparison to Indianapolis (see figure 2). If we could identify the factors involved in this delayed onset phenomenon, we would be making considerable progress in identifying possible

prevention strategies. A 5- or 6-year delay in the onset of AD, if accomplished in the United States, would have dramatic public health consequences. It would result roughly in a decline of 30 per cent in prevalence rates.

Prevalence rate figures are, however, dependent on factors other than rates of disease. Differences in these rates may be due to differences in life expectancy or differences in survival of demented and non-demented subjects. Incidence rates — which are the number of new cases occurring over a fixed period of time — are a better indication of true rates of illness than prevalence rates. We now have preliminary results from our first two-year incidence study. The incidence rates of AD from Ibadan are much lower than the incidence rates from

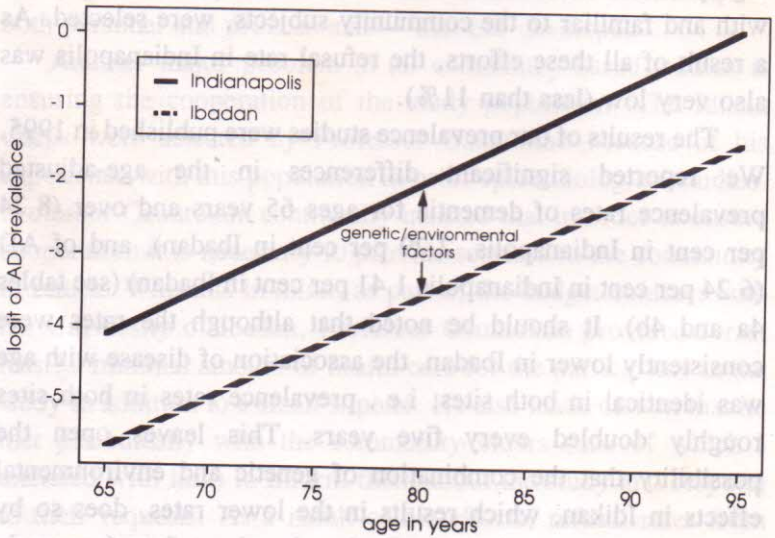

Illustration based on logistic modeling of age-specific prevalence of AD. The slopes for age are the same for both sites suggesting the influences of biological processes fundamental to aging. Genetic/environmental factors account for the differential intercepts

Figure 2. Proposed model of relationship between age, genetic/environmental influences in prevalence of AD

Indianapolis, but because of the relatively small numbers of demented subjects at both sites, it is not yet clear whether these differences are significant. Incidence rates for dementia are 2.41 per cent in Indianapolis and 0.64 per cent in Ibadan; incidence rates for AD are 1.75 per cent in Indianapolis and 0.59 per cent in Ibadan. It will require the results of our ongoing second incidence study to determine if the incidence rates are indeed significantly different between sites.

If, as we suspect, there is a true difference between the rates of AD in Indianapolis and Ibadan, what could account for the differences? We have now conducted a series of studies on risk factors and the occurrence of dementia — especially AD — and poor performance in the screening tests in both Indianapolis and Ibadan. In Indianapolis, in addition to age, a higher risk of developing dementia or AD was associated with low level education, living in a rural community during childhood, a family history of dementia, and a history of stroke. A weak association between possession of the ε4 allele and AD was observed in African Americans, weaker than that reported in other populations, being present only in those subjects with the ε4ε4 genotype. A history of smoking, taking anti-hypertensive medication and small amounts of alcohol appeared to have some protective effects on the subjects in Indianapolis.

In contrast, so far in Ibadan we have been unable to identify any additional risk factor of AD apart from age. In particular, the possession of the ε4 allele of *APO*E appears not to increase the risk of AD in the Yoruba subjects. This raises the possibility that the presence of other factors, either environmental or genetic, may reduce the *APO*E ε4 associated risk of AD in populations of African origin. We are actively involved in the search for these factors at present. The *APO*E protein is involved in the cholesterol transport system. One striking difference

between the populations is their diets. This is reflected in lower cholesterol levels found in the Yoruba in comparison to the African-American population (mean cholesterol levels in the Yoruba, 166 mgs/ml; mean cholesterol levels in African Americans, 220 mgs/ml). It is possible that there is some dietary interaction, perhaps involving cholesterol or other lipids, which in association with *APO*E accounts for the differences in rates of illness between sites. It is also possible that the relative lack of vascular risk factors by itself in the Yoruba may play an important role in modifying disease onset in that population.

In summary, we are pleased with the progress we have made in the Indianapolis-Ibadan project. Overcoming the major methodological problems facing our research teams was in itself no mean accomplishment. We now have preliminary evidence that rates of AD differ between the populations and we have already identified possible genetic and environmental explanations for these differences. We have excellent faculty and staff at both sites, a legacy of Professor Osuntokun. We are looking forward to our continued exploration of risk factors in these populations and hope that our data will assist in the development of both aetiological theories and prevention strategies against AD.

Table 4a. Prevalence of dementia (in %)

Age Group	Ibadan	Community	Indianapolis Nursing Home	Combined
65-74 95% confidence limits	0.86 (0.40 to 1.32)	1.83 (1.11 to 2.55)	45.83 (25.90 to 65.76)	2.62 (1.83 to 3.41)
75-84 95% confidence limits	2.72 (1.62 to 3.81)	6.73 (5.07 to 8.39)	72.22 (57.59 to 86.86)	11.43 (9.56 to 13.29)
85+ 95% confidence limits	9.59 (2.82 to 16.37)	17.07 (12.55 to 21.59)	76.32 (62.80 to 89.94)	32.44 (27.59 to 37.29)
Overall Age Adjusted 95% confidence limits	2.29 (1.17 to 3.41)	4.82 (3.66 to 5.99)	Not Applicable	8.24 (7.09 to 9.40)

HC Hendrie, BO Osuntokun, KS Hall et al. 1995.

Table 4b. Prevalence of Alzheimer's disease (in %)

Age Group	Ibadan	Community	Indianapolis Nursing Home	Combined
65-74 95% confidence limits	0.52 (0.11 to 0.92)	1.15 (0.56 to 1.73)	25.00 (7.69 to 42.31)	1.58 (0.92 to 2.22)
75-84 95% confidence limits	1.69 (0.85 to 2.53)	4.99 (3.46 to 6.52)	47.22 (30.92 to 63.52)	8.02 (6.18 to 9.86)
85+ 95% confidence limits	5.91 (2.30 to 9.53)	14.99 (10.54 to 19.45)	68.42 (53.64 to 83.20)	28.85 (23.80 to 33.91)
Overall Age Adjusted 95% confidence limits	1.41 (0.62 to 2.20)	3.69 (2.60 to 4.77)	Not Applicable	6.24 (5.13 to 7.34)

Synopsis

It was a great honour, privilege and pleasure for me to have had the opportunity of working with Professor Osuntokun during the last years of his life. Professor Osuntokun's accomplishments in neurology, medicine and public health will long be remembered. I hope that the results of our ongoing Indianapolis-Ibadan project, which was very much his brain child, will be considered as one of these enduring accomplishments.

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Professor B.O. Osuntokun's works constitute a significant landmark in the history of the Medical School, University of Ibadan. It eloquently illustrates the heights attainable through sustained diligence and a robust, vibrant intellect in a literally science-unfriendly environment. Kayode did not see a Bunsen burner before entering the University of Ibadan, but rose to become one of Africa's most outstanding medical scientists, a scholar uniquely endowed with the gifts of profound erudition, intense dedication and prodigious energy. He touched nothing that he did not adorn.

A star performance in his undergraduate finals at Ibadan, in 1961, launched him into a remarkable career in medicine. Tutelage under some of Britain's leading clinical scientists of the day (Professor Harold Scarborough in Cardiff and Professor Henry Miller in Newcastle) ensured a sound template in Neurology and effortless ease with the British Membership of the College of Physicians. Windows of opportunity began to open one after another as Kayode's talents blossomed.

Returning to Ibadan in the mid-60s he set out to put African neurology on the global map, first by describing the natural

history of a number of neurological disorders in Africa. He then went on painstakingly to address, through a series of elegant clinical and biochemical studies, the simmering conflict in our understanding of the aetiopathogenesis of an intriguing form of ataxic neuropathy peculiar to sub-Saharan Africa linking it with toxicity of cyanogenetic glycosides in cassava. He took the neuropathies: epilepsy, cerebrovascular disorders, migraine and diabetes mellitus one by one, producing for each a classic treatise, with a tropical flavour, in some of the world's leading clinical and neurological journals. In subsequent years he turned his energies to Community Neurology and the Dementias of the Elderly. Whether at conference presentations, guest lectures, in chapters in books or as part of the over 300 publications in learned scientific journals, Kayode spoke or wrote with unusual depth and clarity, making original observations and indicating nuances of departure from established teaching.

In his global travels he can best be described as the *Marco Polo of African Neurology*, for there was hardly a world capital he did not visit to lecture. Such intense scientific activity inevitably resulted in a glittering array of prizes and distinctions, of which we can only name a few - The Sir Langley Memorial Prize for the best paper in Tropical Medicine (1968-71), The Murgatroyed Prize of the Royal College of Physicians of London for important contributions to Science, the Practice of Medicine in the Tropics (1977) and The Dr. Charles R. Drew World Medical Prize Award in 1989.

To these remarkable attributes we must add his foray into the wider turf of medical administration, medical education and health services research. Administration presented to him the exciting challenges of the Provostship of the famous Aro Neuropsychiatric Hospital and Chief Medical Director of Nigeria's premier teaching hospital — The University College Hospital at Ibadan. Medical Education earned him the Deanship of the Ibadan Medical School (1974-78), a tenure notable for a rapid expansion of undergraduate intake, physical consolidation and curricular development. Health Services research provided for him a pivotal position in the WHO Global Advisory Committee on Health Research (GACHR), that body's most prestigious health research policy organ.

Osuntokun's contributions as a clinical scientist to the work of the WHO will be difficult to surpass. With 120 Consultations as Temporary Adviser, Short-Term Consultant, and as Member of Expert Committees in a wide variety of subjects — at Headquarters in Geneva (sixty visits in 20 years) and at all of the Regional Offices — he straddled the vast expanse of WHO's activities like a colossus, eventually becoming the longest serving Member and Chairman of the GACHR. His term as Chairman of the global committee was notable for positive development following in the tradition of his predecessors, some of whom are Nobel Laureates. His interventions were invariably mature and sensible, always demonstrating a sound grasp of the subject and a human and humane perspective in proffering suggestions and solutions.

Back home in Nigeria, Professor Osuntokun's outstanding achievements were well acknowledged in the award of **Officer of the Federal Republic** (OFR) of Nigeria in 1978, and the **Nigerian National Merit Award** (NNMA) in 1984. It was largely through his academic and professional stature that Ibadan came to be designated by the Nigerian government as a Centre of Excellence in Neurosciences. Indeed, the Dementia project which death found in his hands represents an excellent example of a cross-cultural collaborative effort between Ibadan and Indiana University, and has attracted substantial funds from the National Institutes of Health in Bethesda, U.S., immense international prestige and considerable epidemiological experience to Ibadan. This project has come up with a number of fundamental observations in a virgin but critical area of research into the ageing process in a developing world milieu.

He is survived by his wife Olabopo, herself an accomplished Professor of Ophthalmology at the University of Ibadan, and five children, two of whom are medical doctors.