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From Genes to Prevention: Epidemiology of Alzheimer's Disease. Colloquium of IPSEN Foundation May 25, Paris, France

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In the next 50 years, Alzheimer's disease (AD) is likely to become one of the world's largest public health problems, second only to cancer, unless ways of preventing the disease or treating its preclinical stages are found. Prevention requires the early identification of likely sufferers and determination of the risks that predispose them to AD, information that comes only from large-scale and long-term studies of populations. The progress made in such epidemiological studies and the questions that remain to be answered were the topic of this year's colloquium on Alzheimer's disease, organized for Foundation IPSEN by **Richard Mayeux** (Columbia Univ., New York) and **Yves Christen** (Foundation IPSEN, Paris) and held in Paris on May 25, 1998.

Unlike most of the IPSEN Alzheimer's colloquia, which concentrate on the details of the disease mechanism, the focus of this discussion was the people who have or may develop AD and other dementias. Because of the problems of establishing a clear diagnosis of AD during life, much of the discussion dealt with dementia rather than specifically with AD, although most speakers considered about 80% of the cases in their samples to be AD.

Population studies are essential for determining how best to provide for and treat sufferers in the future, but are also providing valuable pointers to the causes of dementia and in some cases even to potential treatments. Results are now available from several large long-term studies of populations in the USA and Europe, as well as some smaller comparisons of groups with different ethnic or cultural backgrounds. Although these studies are not directly comparable because of differing designs and criteria, they point inescapably to a large increase in the number of people with the disease as the population ages. As important as it is to observe who has the disease (prevalence) and who is getting it (incidence), the work has now moved into a more sophisticated analytical phase (Mayeux), revealing indicators of early disease, and genetic and environmental risk and protective factors. Perhaps more significant in the long term, the ground is being prepared for the time when preventive measures become available by opening up a debate on both the practical and ethical issues sur-

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rounding prevention (**T. Radebaugh**, Reagan Foundation, Washington D. C.; **D. Evans**, Rush Presbyterian St. Lukas Medical Center, Chicago). We present here a broad overview of the riches of data and ideas presented during the day.

PROJECTIONS

As we are all living longer, the elderly population is steadily increasing. In the USA, the number of people over 65 is expected to more than double between 2000 and 2050. In the developing countries, figures are less secure but a substantial increase in life expectancy is anticipated in the next 50 years. As the prevalence of dementia is generally agreed to increase with age, to at least 40% of those aged 95, **R. Katzman** (Univ. California, San Diego) and **A. Hofman** (Erasmus Univ., Rotterdam, The Netherlands) estimate based on current prevalence figures 200 million cases of dementia by 2050, 9.2 million of them in the USA and about 137 million in the developed countries. By 2050, the cost of this burden for the USA is estimated at 383 million US dollars per year (1996 value); worldwide the cost could reach several billion dollars (**P. Fox**, Univ. California, San Francisco).

These figures assume that detection, prevention, and treatment of dementia remains as it is today. On this basis, the US alone can expect 2.5 million new cases in 2050, second only to 2.7 million new cases of cancer, which emphasizes the urgent need to develop preventive strategies. But effective prevention depends on accurate figure. Sources of error include: the criteria for diagnosis of dementia and differentiation between AD and other dementias; the selection of the groups for study and who in the group are willing to participate; and the way cultural differences are taken into account (Katzman, Evans, Radebaugh, **H. Hendrie**, Indiana Univ., Indianapolis). The projections for developing countries are based on very limited samples and little information is available for Africa (Katzman, Hendrie). Lastly, no one knows what the effect will be of the enormous social and cultural changes that are occurring in both developed and developing countries (Radebaugh).

PREDICTION

Identifying risk factors is a big step towards determining who is likely to become demented and when. Age is the best established risk, with incidence increasing exponentially after the age of 75; still only a proportion of the elderly become demented. There are some indications that the over-75s may divide into high- and low-risk groups (Mayeux). Genetic makeup is the best known of other risk factors but a range of predisposing diseases and so-called environmental factors are being identified that also seem to contribute.

People with mutations in the genes for amyloid precursor protein and presenilins 1 and 2 almost always develop AD, usually before age 65 — their risk is close to 100%. Mayeux termed these the deterministic genes and yet, because their mutations are rare, together they contribute less than 1% to the total risk in the population

(**C. Van Duijn**, Erasmus Univ., Rotterdam). Much more significant are versions of genes, termed susceptibility genes, that either increase the individual's risk of getting AD or are protective. These are thought to help determine how the individual copes with exposure to various (mostly unidentified) risk factors encountered throughout life (Mayeux).

The only well-established susceptibility gene is that coding for apolipoprotein E (ApoE), although a second susceptibility gene on chromosome 12 has recently been reported by Periak-Vance and Roses. Those carrying the ε4 allele of the ApoE gene are known to have a greater risk of developing AD over the age of 65 than those with other versions of the gene, but recent data from the Rotterdam study of 8000 people (55 years old) has shown that the ε4 allele also contributes substantially to increased risk of developing early-onset AD (Van Duijn). Even so, the well-known genes account for only about 60% of those with AD. It seems increasingly unlikely that other genes with a large effect will now be found.

Risk factors rarely act in isolation, however, and AD is a prime of example of a disease with a "web of causality," rather than simple, single causes (Evans). The alternative, and more probable, explanation is that a complex pattern of small changes in many genes contributes to the chance that an individual will develop AD (Mayeux, Van Duijn). The effects of these genes are also likely be dependent on the circumstances of the individual, including race and culture, as well as local factors such as diet and exposure to toxins. Studies of ethnic groups, migrants, and isolated populations are helping to untangle the interactions between the various factors. Already the risk associated with carrying one ε4 allele is known to differ for caucasians, hispanics and afro-americans (Mayeux), a good example of how the total genetic makeup can influence the outcome of carrying a susceptibility version of a gene.

A striking association between cardiovascular diseases and dementia that does not depend on genes directly associated with AD has recently been established in studies in Holland and Sweden (Hofman; **I. Skoog**, Sahlgrenska Hosp., Gothenburg, Sweden). In the Rotterdam study, the incidence of dementia was substantially higher for those with diabetes mellitus, atherosclerosis, and atrial fibrillation (Hofman) and a prospective study treating patients with hypertension is underway in Sweden (Skoog). Smoking, which increases the risk of cardiovascular disease, has been controversial as a risk factor for AD because of claims that nicotine might protect the brain pathways dependent on the transmitter acetylcholine. In the Rotterdam sample, smoking considerably increased the risk of dementia, except for smokers with the ApoE ε4 allele, whose risk was lower than expected (**M. Breteler**, Erasmus Univ., Rotterdam). This clear example of how factors can interact also demonstrates how misleading studies can be when the influences of different variables are examined in isolation.

Life history must also be considered. The Paquid study in southwestern France has established a higher risk of dementia among those with lower educational attainment (**J.-F. Dartigues**, Inserm Unit 380, Bordeaux, France). In this population, the incidence of dementia was higher in women than men only over the age of 77, compared with a study of 18,500 people 65 years old in England, where considerably more women than men already had dementia (**C. Brayne**, Univ. Cambridge, UK).

PROTECTION

But not everything in life is bad for you: in the Pasquid sample, those who gardened, traveled, and had hobbies such as knitting were at significantly lower risk of dementia; a moderate consumption of wine also seemed to help (Dartigues), as did an active sex life over the age of 70 (Skoog)! Two therapies for other conditions also point to possible protective measures: estrogen replacement for menopausal women and non-steroidal anti-inflammatory drugs (NSAIDs) used to treat arthritis.

Several small studies have now shown that taking estrogen as part of hormone replacement therapy reduces the risk of dementia by as much as 30%, although one well-designed study found no effect. Estrogen seems a good candidate for protecting the brain, as it has receptors in the brain and affects cerebral blood flow and metabolism, as well as the formation of new synapses and the death of nerve cells. Verbal memory improves in women taking estrogen, which is also anti-inflammatory and protects against damaging effects of oxidation (**V. Henderson**, Univ. Southern California, Los Angeles).

The discovery a few years ago that dementia is less common among arthritis sufferers led to the idea that AD is an inflammatory condition that might respond to anti-inflammatory drugs. Although not all studies are in agreement, a longitudinal study of men over 40 in Baltimore has shown a 50% reduction in risk among those taking NSAIDs for more than 2 years. Aspirin had little effect, perhaps because normal doses are too low to suppress the neutrophils that are activated in inflammatory conditions. More promising for the future may be drugs that inhibit cyclooxygenase type 2 (Cox-2), an enzyme that promotes inflammatory reactions and is present in increased amounts in the cerebral cortex of AD victims (**C. Kawas**, Johns Hopkins School of Medicine, Baltimore).

PREVENTION

The use of estrogens and anti-inflammatory drugs as protective strategies offer the first feasible therapies for primary prevention of AD, that is, stopping the disease from developing. Intervention in the preclinical or early stages of the disease (secondary prevention), for instance with drugs to treat cardiovascular problems, and even treatment of those with full-blown AD (tertiary prevention), could help to delay decline and reduce the severity of symptoms (Brayne). Projections from current incidence and prevalence data indicate that delaying onset of clinical disease by 5 years could halve the number of new cases, and even delaying onset by 6 to 12 months could have a substantial effect (Kawas). In the long run, the case for prevention may be stronger on humanistic than economic grounds, as considerable resources will still be required for the increased numbers of frail elderly who will remain healthy (Evans).

Primary and secondary prevention are still some way off because of the difficulties of identifying those at high risk (Brayne, Evans, Skoog). Not only is accurate diagnosis important to target resources effectively but it is also necessary not to alarm and

distress patients with false positives. For instance, despite the high risk associated with the ApoE ε4 allele, not all carriers develop AD, so it is probably unethical to screen for the allele (Skoog). Differential diagnosis, especially to distinguish between AD and vascular dementia remains difficult, time-consuming, and expensive, and subjects patients to the discomforts of brain scans and lumbar punctures.

Good prevention will require acceptable, sensitive, and easily applied tests for preliminary screening. Sensitive psychometric test batteries are now available (Evans) and are being modified to make them more appropriate for use with different cultural groups (Hendrie). The results of these could be combined with known risk and protective factors to identify people at greatest risk (Brayne). One serious concern is the poor identification of mild dementia by primary care physicians, who are most likely to encounter patients in the early stages of the disease.

Developing effective prevention, though essential and urgent, will not be easy. A comparison was made to the slow progress in the prevention of heart disease, which has advanced by many small steps over the past 50 years. The severity of the projected problem with AD means that we do not have as much time to develop good preventive strategies, but the best way forward is still likely to be small steps. These could have an empirical basis rather than waiting for a full understanding of the pathogenesis of the disease. A strong case was put forward for beginning random prevention trials, perhaps with estrogen (Evans). However, a balance must be found between moving on rapidly and the possibility that failures in particular trials lead to reduction in resources and reluctance among patients to participate in clinical trials. In the meantime, we may want to take prevention into our own hands, as Skoog closed by suggesting, with wine, sex, and possibly smoking!