Chapter 1
Dementia and the Health of the Nation

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Introduction: The Scale of the Dementia Challenge

It is said that when Dr Alois Alzheimer made his presentation entitled "On a peculiar disease process of the cerebral cortex", in which the clinical and neuropathological findings in his patient, Auguste D., were first delivered [1], the audience at the 37th Conference of the South-West German Psychiatrists in Tübingen on that November day in 1906 made no comments and asked no questions. Even following Alzheimer's eponymous immortalization by Emil Kraepelin in the 8th edition of the latter's psychiatry textbook published in 1910, and the publication of the first cases in the English language in 1912 by Solomon Carter Fuller [2], "Alzheimer's disease" (AD) continued to be viewed as a very rare presenile form of dementia. Indeed, it was not until the equation of "senile dementia" with "Alzheimer's disease" in the 1960s and 1970s, based on the work of Tomlinson and

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Roth in the United Kingdom [3] and Robert Katzman in the Unites States of America [4], that the prevalence, morbidity and mortality of this condition was realised, transforming AD from a rare eponymous condition to an issue of major social, economic, and political significance [5].

As increasing age is recognised to be the major (unmodifiable) risk factor for the development of AD and other neurodegenerative forms of dementia, it is immediately obvious that the prevalence of dementia will increase as the population ages. Much research effort has been expended in recent years in epidemiological studies of dementia prevalence and incidence, especially of AD. The large majority of these investigations have indicated an increasing burden of disease, with patient numbers predicted to increase dramatically worldwide in the coming decades [6–8]. Alongside the human cost, to both patients and their carers, these numbers will have significant societal and financial cost implications [7, 9]. For example, a 2010 global cost of illness study suggested a "base case option" figure of US$604 billion, equivalent to the 18th largest national economy in the world (between Turkey and Indonesia), and larger than the revenue of the world's largest companies (Wal-Mart, Exxon Mobil) at that time. In high income countries, which accounted for 89% of the costs but only 46% of dementia prevalence, this was mostly due to the direct costs of social care, whilst in low and middle income countries, which accounted for only 11% of the costs but 54% of dementia prevalence, this was mostly due to informal care costs [9]. Such figures indicate the need to take action now, if possible, the moreso if one factors into this consideration the likelihood that many dementia cases remain undetected in the community (meta-analytic pooled rate of undetected dementia in 23 suitable studies was a staggering 61.7%) [10].

This grim epidemiological picture is compounded by the current absence of effective treatments for dementia. Although cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine are licensed for the symptomatic treatment of AD in many countries, their effects are variable and at best modest, with no evidence for a disease

modifying effect. Experimental pharmacotherapies, many developed on the basis of the predictions of the amyloid hypothesis of AD pathogenesis, have failed to translate to the clinical arena, despite initially encouraging findings in animal models of AD.

Although the possible discovery of effective disease modifying treatments for dementia cannot be ruled out, it seems unlikely that the traditional, "reactive", model of disease management – in which patients present with symptoms which doctors evaluate, diagnose, and treat – will suffice in this context. Something more proactive is going to be required in the future: at the current time it seems likely that preventative measures constitute a more viable approach. Certainly this has been an increasing subject of interest to dementia researchers in recent years [11, 12]. Such preventative measures will require a significant change in the approach to medical management, also encompassing political action.

Dementia Has Predementia and Preclinical Phases

In this context, it is worth remembering that dementia is a disease process rather than an event (with perhaps the exception of the very rare instances of "strategic infarct dementia" affecting cognitively eloquent structures). For example, in the case of AD it is evident from longitudinal studies of individuals harbouring deterministic mutations for early-onset disease that changes are occurring in the brain for many years prior to the onset of the clinical symptoms of cognitive change [13, 14]. The presymptomatic or preclinical phase is succeeded by a predementia or prodromal phase (nomenclature of Dubois et al. [15]); the latter has previously been characterised as "mild cognitive impairment" (MCI), and further categorised according to the neuropsychological phenotype as amnestic MCI, single non-memory domain MCI, or multiple domain MCI. However, some authorities prefer to diagnose "prodromal AD" or

Table 1.1 Biomarkers of AD at any disease stage

Diagnostic markers (specific for presence of amyloid or tau pathology):
Cerebrospinal fluid:
Reduced Abeta1–42
Raised total-tau protein or phospho-tau protein
Amyloid Positron Emission Tomography (amyloid PET):
Deposition of Abeta1-42
[In development: *Tau Positron Emission Tomography (tau PET):* Deposition of tau protein]
Progression markers (downstream markers, lacking pathological specificity):
Fluorodeoxyglucose Positron Emission Tomography (FDG PET):
Cortical hypometabolism, especially temporoparietal distribution.
Magnetic Resonance (MR) imaging:
Atrophy of medial temporal cortex and hippocampus

early AD when possible, based on changes in disease 'biomarkers' that can be identified radiologically or biochemically (see Table 1.1) and which are now incorporated into diagnostic criteria for AD [16].

Other dementing disorders also have a symptomatic but predementia phase (e.g. MCI in Parkinson's disease dementia/dementia with Lewy bodies, vascular dementia, frontotemporal dementia [17–19]) and presymptomatic or preclinical phases. Hence there is a window of opportunity, lasting potentially decades, when interventions might slow or halt the pathogenetic processes, thereby delaying or preventing the clinical features of dementia.

Prevention: Individual Risk Prediction

Accurate, individually tailored, prediction of AD diagnosis cannot currently be made, with the exception of relatively rare individuals with a family history of early-onset AD with

Table 1.2 Genetic factors in AD

Early-onset familial AD
Autosomal dominant disease, deterministic mutations in genes coding for:
Amyloid precursor protein (APP)
Presenilin 1 (PSEN1)
Presenilin 2 (PSEN2)

an inheritance pattern in keeping with an autosomal dominant disorder. Mutations in three genes have been shown to be deterministic for early-onset familial AD (Table 1.2), namely amyloid precursor protein (APP), and presenilin 1 and 2 (PSEN1, PSEN2). If a pathogenic mutation can be defined in one or more affected family members, genetic counselling and predictive testing (in that order), using a model first developed in Huntington's disease, may be undertaken in at-risk individuals ("asymptomatic-at-risk AD" [15]). A similar approach may be taken in familial frontotemporal dementia. It should be emphasized that such cases constitute only a small proportion of all dementia, and moreover that there is at this time no effective disease modifying treatment that can be recommended to an individual with a predictive dementia diagnosis. The grim prospect of the future inevitability of disease may understandably discourage some at-risk individuals from accessing predictive testing.

In addition to deterministic genetic mutations, a number of genetic predisposing factors, of themselves neither necessary nor sufficient to cause AD, have been identified. Of these, the best known relates to apolipoprotein E (ApoE) genotypes, one of which (epsilon 4) increases AD risk, whereas another (epsilon 2) reduces it. The use of genome wide association screens (GWAS) examining many thousands of patients and controls has broadened the number of identified possible genetic risk factors for AD [20, 21].

GWAS studies have produced large datasets which allow genetic information to be matched with clinical and laboratory information and from which an epidemiological framework for individual risk prediction can be constructed. For

example, a recent study [21] constructed a "polygenic hazard score" (PHS) for late-onset AD, the most common form of the disease, which incorporated 33 single nucleotide polymorphisms (SNPs) reported to increase the genetic risk of AD in case-control studies, including two variants of the ApoE gene. The PHS successfully stratified individuals into different risk strata in replication studies undertaken in independent patient samples. The age of AD onset predicted by the model was strongly associated with the actual age of onset. Likewise, PHS also strongly predicted time to progression to neuropathologically defined AD. Individual genetic profile and age could be translated into incidence rates, with PHS-predicted incidence strongly associated with empirical progression rates. In other words, individual differences in risk of developing AD could be quantified as a function of patient genotype and age. PHS was significantly associated with decreased CSF Abeta1–42 and increased CSF total-tau; and with greater neuroradiological volume loss in the medial temporal lobes [22].

The implications of this PHS, or any future instrument generated by similar means, are many [22, 23]. It may be used to estimate individual differences in AD risk across a patient's lifetime and to quantify the yearly incidence rate for developing AD. Such information might potentially be used at the individual level for the purpose of future planning, and at the collaborative level to enrich patient cohorts entering prevention and therapeutic trials (previous clinical trials may have failed, at least in part, because of inclusion of age-matched controls who were at high risk of progression to disease).

The approach used in this study is illustrative of an emerging trend, namely the development of "bioprediction" of brain disorder. This represents a reorientation of the medical concept of "disorder" which rejects the old binary or categorical formulation (disorder/normalcy) in favour of a probabilistic model based on present and future risks of harm. Such an approach is justified in part by the belief that disease biomarkers will not map cleanly onto clinical diagnostic categories. Matthew Baum has explored the bioethical issues, and

has proposed a "probability dysfunction" model in which disorders are conceptualised as graphs of probability over time, the area under which would help to separate out self-limiting disorders from those with low probabilities of harm over longer time periods. "Risk banding", based on the shape of the probability function, is the strategy advocated to determine the necessity or otherwise for response/intervention [24]. PHS may be seen as a probability function which might be used to address individual risk of developing AD [23].

Prevention: Population Screening

The highly sophisticated methods required for genotyping and risk prediction may prove difficult to scale up to the population level, even though costs of genetic testing have fallen significantly in recent years. Hence, other strategies for the identification of individuals either in the early stages or at risk of dementia, and hence candidates for any identified disease modifying intervention, require exploration. To prevent dementia requires some form of screening process. How this might be effected requires careful consideration.

The classic criteria for disease screening were published under the auspices of the World Health Organisation (WHO) nearly 50 years ago (see Table 1.3) [25]. Guidelines and criteria for developing screening programmes have also been issued, such as those from the UK National Screening Committee (https://www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc).

Of these conditions, some are fulfilled for dementia, such as the importance to public health with significant economic cost implications [5–9]. It is also clear that the natural history of most forms of dementia encompasses a presymptomatic/preclinical phase, with disease evolution occurring over many years before clinical presentation [13, 14, 17–19]. However, many other screening criteria are not (yet) fulfilled for dementia. None of the available pharmacotherapies for AD have been shown to be more beneficial when applied at the presymptomatic/preclinical stage compared to the later

Table 1.3 WHO screening criteria

The disease/condition sought should be an important public health problem.
There should be a recognisable latent or presymptomatic stage of the disease.
The natural history of the disease should be adequately understood.
There should be a treatment for the condition, which should be more beneficial when applied at the presymptomatic stage compared to the later symptomatic stage.
There should be a suitable test or examination to detect the disease with reasonable sensitivity and specificity.
The test should be acceptable to the population.
The healthcare system should have the capacity and policies in place to test for the condition and deal with the consequences.
The cost of case finding, including diagnosis and treatment of patients diagnosed, should be economically balanced in relation to possible expenditure on medical care as a whole.
Case finding should be a continuing process and not a "once and for all" project.

symptomatic stages. It is not clear whether healthcare systems have the capacity and policies to test for dementia and deal with the consequences, nor that the cost of case finding, including diagnosis and treatment, would be economically balanced in relation to possible expenditure on medical care as a whole [26].

Hesitation about the initiation of population screening, particularly in the absence of a test or examination to detect disease with reasonable sensitivity and specificity (with the risk of large numbers of either false positive or false negative diagnoses), is understandable [27, 28]. There are many existing cognitive screening instruments [29]. Initially these were pen and paper tests but now are increasingly available as online instruments, including web-based apps, which might even be used in the future for patient self-assessment. However, the many shortcomings of such cognitive screening instruments are well-recognised, not least that tests which are too sensitive will identify many false positives

whilst tests which are too specific risk false negative diagnoses, both of which have a cost (emotional and financial). Furthermore, whether these screening instruments can reduce the acknowledged "dementia diagnosis gap", the difference between numbers of observed and expected cases of dementia (perhaps 50% in the UK [30]), let alone those at-risk of dementia, remains to be shown [31].

Dementia and Cognitive Impairment in the Surgical Population

A number of risk factors for AD have been identified which might form the basis for effective screening and possible intervention in populations presenting for surgery. These include vascular risk factors, such as midlife hypertension and hypercholesterolaemia, and diabetes mellitus. These vascular risk factors suggest possible cerebrovascular components in AD pathogenesis, and indeed there is neuropathological evidence of overlap between AD and vascular dementia, indicating that these changes most usually lie on a continuum or spectrum rather than representing "pure" conditions [32]. Amyloid PET imaging, an AD biomarker, shows amyloid deposition is associated strongly with traditional cardiovascular risk factors [33]. Such findings raise the possibility of modifiable risk factors for dementia (AD and vascular) which may be addressed, as for cardiovascular disease, even at the primary care level. Risk scores for prediction of dementia have been previously constructed, based on recognised mid-life vascular risk factors such as hypertension and hypercholesterolaemia (Fig. 1.1) [34].

In addition to these risk factors, it has been questioned whether the stress response of surgery may affect long term cognitive function. Post-operative delirium has been associated with more rapid cognitive decline, and more severe delirium with a greater rate of cognitive decline [35]. Surgery may also "unmask" pre-existing but clinically undeclared neurodegenerative disease giving the impression of "acute onset" [36].

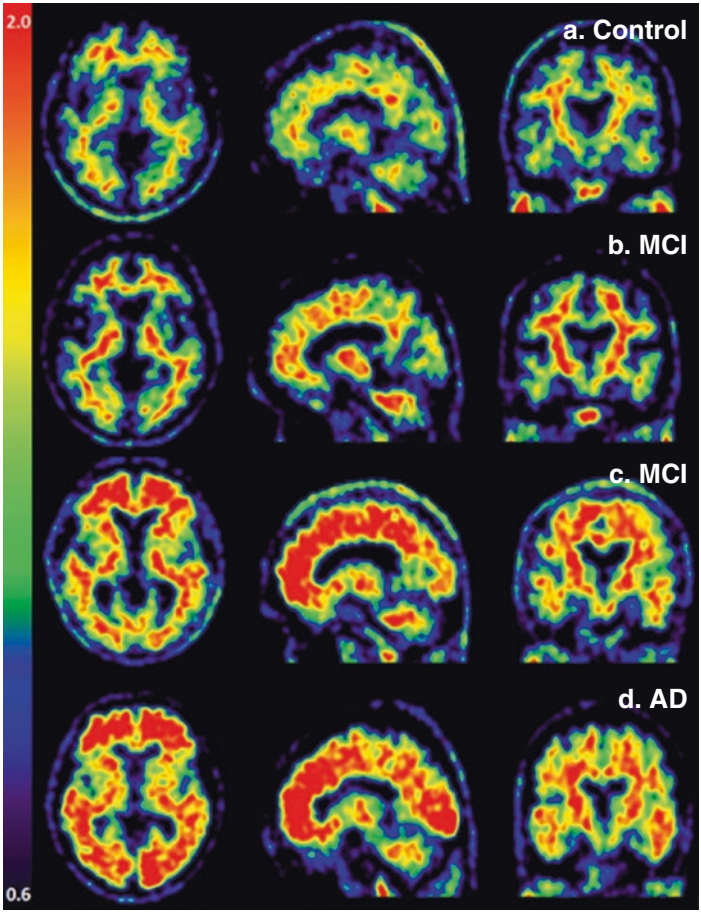

Figure 1.1 Amyloid (18F florbetapir) PET imaging, showing from left to right axial, sagittal and coronal brain images. Negative scans in a normal control subject (**a**) and a mild cognitive impairment (MCI) patient (**b**); positive scans in another MCI patient (**c**) and a patient with Alzheimer's disease (**d**). (Reproduced with permission from Eur J Nucl Med Mol Imaging. 2012 Apr;39(4):621–31. doi: 10.1007/s00259-011-2021-8. Epub 2012 Jan 18.)

The UK National Institute for Health and Care Excellence (NICE) issued a guideline in October 2015 whose title suggested a focus on dementia prevention, with recommendations

aimed at the promotion of a healthy lifestyle, e.g. stop smoking, be more physically active, reduce alcohol consumption, adopt a healthy diet, and achieve and/or maintain a healthy weight [37]. There is some preliminary evidence of falling overall prevalence and incidence of dementia in the UK [38, 39]. Whether this reduction is a consequence of improved prevention and treatment of vascular risk factors, or due to other factors (e.g. better education, living conditions) is currently unknown [39]. Further longitudinal epidemiological studies may be required to answer such questions, but these are time-consuming and expensive. Pending definitive answers, it would not seem unreasonable to promote such interventions as likely preservers of brain health [40, 41]. It is argued that such "upstream primary prevention" has the largest effect on reduction of later dementia occurrence and disability [39].

Conclusion

The anticipated increase in the numbers of individuals with dementia as the world population ages threatens to overwhelm existing health and social care services. Interventions applied now which might contribute to the prevention of this eventuality should be welcomed. However, no intervention has yet been conclusively proven to reduce dementia risk at the individual or population level. Nevertheless, the identification of modifiable risk factors, such as midlife hypertension, hypercholesterolaemia, and diabetes mellitus, suggests that a vigorous screening policy to tackle these issues might pay long term dividends. Targeting individuals falling within a high risk band of a probability function, based on age and genotype, might ensure cost effective intervention.

Public health problems require public health solutions, which require political as well as clinical resolve and action. To this end, it is heartening to see initiatives to address these problems sponsored by the UK government, some with prime ministerial imprimatur [42–44], and by the international community (G8 nations) [45], even if these are by nature aspirational and relatively uncosted. It will require

long-term commitment and funding from many sources to ensure the optimum management of dementia and to guarantee the brain health of all populations.

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