Editorials

Dementia:

is the biopsychosocial model vindicated?

THE PHARMACOLOGICAL MODEL AND DEMENTIA AS DISABILITY

We know so much more about dementia syndrome than we did 20 years ago, but we can do little more for it medically. A *BMJ* editorial of 1 October 1983 entitled 'Dementia: biological solution still a long way off' still holds good. The pathological model built around a neurone-centric, linear cascade initiated by amyloid and leading to the dominant subtype of dementia, Alzheimer's disease (AD), is wrong. This direct causality is incompatible with clinical observations,[1] and has failed to produce any significant pharmacological therapies. Not only are there no disease-modifying drugs but also the symptom modifiers, cholinesterase inhibitors and memantine, yield clinical benefits that are negligible at a population level.[2] The research community acknowledges that a single cure for AD is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered.[3]

This is a pessimistic picture, but only if all research is focused on cellular mechanisms. We can be more optimistic if we frame dementia syndrome as a disability (the gap between environmental demand and personal capability), understand the epidemiology of cognitive impairment and the clustering of dementia with other conditions, and appreciate new findings about brain protection.[4]

NEW THINKING ON DEMENTIA HARMS

Epidemiological evidence about the origins of dementia syndrome gives us some clues about what to do, suggesting that preventive activities against heart disease protect the brain, and may even be showing a reduction in incidence and prevalence. Dementia syndrome and its subtypes seem to arise through the accumulation of harms over the life course, and cluster with other endemic conditions that exacerbate each other synergistically, making 'syndemic' disorders.[5]

Knowledge about the mechanisms protecting brain cells is becoming clearer, as is our understanding of epigenetics, neuroplasticity, and cognitive reserve. For example, learning and recall, and physical exercise, induce neuronal activation through epigenetic modifications, while age-related reductions in glucose uptake by neurones lead to a vicious cycle of degenerative changes, reduced synaptic activity, and further reductions in glucose uptake.

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Poverty in childhood and adolescent environment are associated with higher risk of AD.[5] Areas of the brain showing earliest signs of AD are the same areas that take the longest to mature during childhood and adolescence. Childhood adversity may cause biological vulnerability, increasing the risk of depression and cognitive impairment in later life.

Non-adherence to a Mediterranean diet (MeDi) predicts AD (after adjustment for other risk factors).[6] Other factors implicated in the origins of cognitive impairment include *Helicobacter* infection, sleeping too much or too little in midlife, short leg length (a proxy for poor nutrition), limited education, low status work, and early parental death.[7] Being married, living with others, and not being lonely appear protective,[8] whereas air pollution unsurprisingly is not.[9]

Diabetes trebles the risk of mild cognitive impairment (MCI) and progression to dementia.[10] Both share common abnormalities such as impaired glucose metabolism, increased oxidative stress, insulin resistance, and deposition of amyloidogenic proteins. Persistent smoking from midlife is a risk factor for dementia and its subtypes.[11] Oxi-inflammatory load and cardiovascular risk factor scores, when combined, double the risk of cognitive impairment.[12]

LIFESTYLE CHANGE AS PROTECTIVE FACTOR

Protective factors are becoming more salient. Repressor element 1-silencing transcription factor (REST),[13] which is present in the normal ageing of cortical and hippocampal cells, and lost in MCI and AD, 'switches off' genes promoting cell death and 'switches on' genes protecting against stress. REST levels are increased among people who are ageing healthily, having stopped smoking, changed their diet, and increased their physical activity levels. In other words we are beginning to see — through REST and other factors — the mechanisms that link lifestyle change to neuronal protection.

THE ROLE OF GENERAL PRACTICE IN PREVENTION AND RESEARCH

What are the implications for general practice? First, dementia as a disability may be part of a triad of impairments: cognitive, emotional (depression), and physical (frailty). Other syndemic associations that are visible in clinical practice are with diabetes and heart disease. Because syndemic conditions make each other worse, treatment of one may improve the others, or at least slow deterioration. A holistic approach of the kind long advocated by GPs is needed, as an antidote to specialists' over-concentration on dementia as a discrete entity.

Second, because prevention is more valuable than treatment for most real-world situations, public health approaches involving long-term, low-level activities in civil society are likely to yield more benefit than the current clinic-based activity. Primary prevention will include actions to lift children out of poverty as well as promotion of lifestyle changes among adults. Practical public health examples

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of secondary and tertiary prevention could include dementia support workers, who reduce environmental demands at individual level, and dementia-friendly communities, which reduce environmental demand at a social level.

Third, primary care researchers have opportunities to use general practice databases for large-scale epidemiological studies to explore the life course origins of dementia syndrome. With intervention and implementation studies there is a need for a more coherent research agenda, especially around deciding on the desired outcomes in neurodegenerative conditions. Larger, longer, better-quality studies are needed, while tricky methodological problems like measuring dietary adherence need to be solved.

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