

OCKHAM'S RAZOR

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ALZHEIMER'S DISEASE: THE RISE AND FALL OF A CONCEPT

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1 Prologue

One of the quiet revolutions of the last century or so has been in how we die. For the individual, death is a personal ordeal, which we each must somehow face. Statistically, however, the causes and experience of death are changing. In particular, we are dying at progressively older ages, and age-related diseases are more common, more troubling, and more important. This talk is about one of the most troubling of the trials of age, dementia. Dementia has been recognized for centuries, and has long been regarded as a normal feature of aging. In his *As You Like It*, Shakespeare traced the life of a man from mewling infant to whining schoolboy to sighing lover, to cursing soldier, to pompous middle age and piping old age and then:

*Last scene of all,
That ends this strange eventful history,
Is second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.*
Act II, Scene vii

Until the great public health advances of the late 19th Century, however, most of the dying in all societies, was done by children, overwhelmed by infectious diseases. Age-related conditions of dementia and blindness and muscular weakness and loss of teeth were mixed up in people's understanding, as in Shakespeare's stanza, as senility. And the first step of medical science in devising treatment for the problems of aging was to separate the several aspects of aging, among them dementia, so that each could be understood and treated separately.

By the latter half of the 19th Century, neurologists had identified dementia as a condition separate from just 'getting old'; and they

had distinguished different types of dementia – the dementia caused by syphilis, for example, was distinguished from vascular dementia, which is caused by a series of strokes; and from *dementia pugilistica*, which afflicts boxers who have fought too long. And the neurologists realized that many cases occur in advanced age, without any reason apparent other than age; and they called this *senile dementia*.

2 A dementia too many

Early in the 20th Century, the German neurologists Alois Alzheimer and Emil Kraepelin proposed the recognition of a new form of dementia, characterized by 3 features. First, it appeared in people who were not old, still in their 40's or 50's. Second, it seemed to occur insidiously, without any other known cause of dementia. Third, Alzheimer provided a brilliant description of the pathology of the brain in his cases. Scattered throughout the brains of his patients he saw abnormal blobs of proteins, which are now called plaques, sometimes senile plaques, and sometimes amyloid plaques.

The plaques have become very important, and eventually confusing, to the understanding of dementia. They are abnormal regions where the complex circuitry of the brain has broken down and a range of abnormal proteins has been deposited, and they are used by pathologists throughout the world to diagnose a dementia as Alzheimer's disease. Further, many scientists believe that the cause of the dementia lies in one of the many proteins found in plaques. The protein thought to be the culprit is called amyloid. It is believed to deposit in brain tissue as nerve cells die; and to form a toxic breakdown product called β -amyloid; which then poisons more nerve cells, which die and release their amyloid; and a destructive cycle follows.

This understanding of dementia took over a century to build, but right at the start of these great developments, Alzheimer was convinced that he had identified a new form of dementia. His influential mentor, Emil Kraepelin, agreed; gave the concept his backing; proposed naming the dementia after its discoverer, and Alzheimer's disease – the best known of the dementias - was launched.

3 The distinction dissolves

3.1 Early onset is not distinctive

It had become clear by the 1970's, however, that Alzheimer's idea that he had identified a new, early-onset dementia, was not tenable. Study after study through the middle of the 20th Century had shown that the early onset cases were just early instances of age-related dementia. Alzheimer's idea of a discrete early onset condition has been quietly abandoned and the term Alzheimer's disease is currently applied to age-related dementia, provided the brains shows plaques in sufficient number. A few, genetically driven forms of early-onset dementia have been identified, but we now know, thanks to some clever DNA detective work, that Alzheimer's patients did not carry these genes.

3.2 Co-morbidity – sometimes? Always?

Not yet quite abandoned, but under challenge, is the second of Alzheimer's claims for his dementia, that it occurs without any sign of other known diseases. From the start there has been a debate whether age-related dementia can occur without diffuse disease of the blood vessels of the brain. Kraepelin discussed the issue, way back in 1910 and, in recent studies, estimates of how often vessel disease occurs in age-related dementia vary

from 30% to 90-odd percent, and some scientists have begun to argue that maybe Alzheimer's disease is a vascular disease. The brain atrophies, they argue, because its blood vessels break down, maybe getting blocked, maybe bleeding, in either case starving the brain tissue of blood.

Adding strength to this view is evidence from a quite unexpected source. This was evidence, first reported in the 1980's, that anti-inflammatory drugs taken for other reasons, usually arthritis, are highly protective against dementia. By the late 1990's, a score or more of studies had appeared, from Europe, North America, Japan and Australia, all confirming the point. Take NSAIDs (non-steroidal anti-inflammatories) – aspirin and indomethacin, and several others - and your chances of getting dementia are reduced by 30%, some said; or 50% or more. How these drugs protect against dementia is still debated, but one possibility is that they protect blood vessels against oxidative damage. More recently, the statin drugs – which were developed specifically to reduce cholesterol levels and the atherosclerotic degeneration of vessels – have proved also to be protective against dementia. And finally on this point, there is an important literature on risk factors. Without any assumption about what causes a disease, epidemiologists can analyse what factors seem to be associated with low or high incidence – diet, age, lifestyle. To cut a long story short, the risk factors for dementia are almost identical with the risk factors for diseases of the cardiovascular system, the heart and blood vessels. The case for considering the dementia which Alzheimer and Kraepelin described as a disease of blood vessels is growing.

4 The problem of treatment

Yet another way of assessing our understanding of a disease, is whether it leads to successful treatment. The analysis of the amyloid protein

of senile plaques, although powerful, has not yet led to treatment of dementia to ways of delaying or preventing of dementia. Ways of reducing amyloid deposits in the brain are being devised, and even applied in clinical trials, but not yet with benefit to patients. In the meantime, large-scale prevention is underway in people who, largely for other reasons – arthritis or high cholesterol - are taking NSAIDs and statins. It may be time, respectfully but firmly, to stop looking for treatment for Alzheimer’s disease because Alzheimer’s concept of an early onset dementia with a distinctive, plaque-related cause has failed; it was a distinction too far, which now inhibits the growth of understanding of how much protection is available – now – against dementia.

5 Dementia is a cerebrovascular disease

I became involved in trying to understand the causes of dementia a decade or so ago, when a private charitable trust based in Sydney, the Sir Zelman Cowen Universities Fund, asked me to help manage its research grants program, in which work on dementia had high priority. Through that program, I became aware of the work of a young neuropathologist at the University of Sydney, Karen Cullen, who showed me some of her material from the brains of patients diagnosed with Alzheimer’s disease. In a critical step, she had deliberately searched for signs of bleeding in these brains, using a range of techniques to detect blood residue and relate it to plaques. Her material showed that every plaque in every brain she studied - in young brains where the plaques are uncommon, in older brains, in demented brains where the plaques are numerous - every plaque is the site of a small bleed, a tiny stroke. Her finding confirms the growing evidence that the Alzheimer-like dementias involve vascular disease, and show precisely what is

happening –blood vessels break down in the aging brain, as they do in aging skin, creating first one, then a few, then many dead patches of brain, which we see after death as plaques. A finding as striking as this is rarely accepted without argument, and Karen’s work has struck its share of dismissal and delay. But the papers describing her findings will shortly appear in international journals; and, we hope, a door to prevention, and delay of dementia – half open for over a decade – will be opened more widely.

For Karen’s observations suggest that Alzheimer-like dementias occur because of the breakdown of cerebral capillaries, the smallest blood vessels of the brain. Each breakdown is a microstroke, too small to cause symptoms, which is why the sufferers often have no clinical history of stroke. But as these microstrokes accumulate, their effects accumulate, and the familiar, sad pattern of cognitive loss – loss of memory, then personality - follows. Age-related dementia is a vascular disease. That is why the anti-inflammatory and statin drugs are protective. That is why the risk factors for cardiovascular disease and dementia overlap so extensively. That is where prevention and delay are already available. That is where advances in the design and deployment of drugs which preserve blood vessels should give the long-awaited tools to delay and prevent this slow, troubling destruction of personality, known to family and carers as ‘the long goodbye’.

And that is why I now take a small aspirin tablet daily; at, least, I do whenever I remember.