Is Dementia Inevitable?
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Nearly four and a half thousand years ago, Ptah-hotep, a vizier during the Egyptian Fifth Dynasty, began to forget what had happened the previous day. He was an esteemed writer of maxims, particularly on appropriate behaviour for young men, but unfortunately became increasingly childish himself in his behaviour at night. This might be the first written description of somebody suffering with dementia[i]. Ptah-hotep was elderly and the association of cognitive decline with old age has been widely recognised in literature, from Shakespeare's King Lear “I am a very foolish, fond old man, Fourscore and upward, not an hour more nor less; And to deal plainly, I fear I am not in my perfect mind" and the wonderful writing of Swift describing the struldbruggs in Gulliver's Travels. The struldbruggs, identified at birth by a mark on the forehead, were destined to live forever, but in so doing, lose all mental faculties. And it is not, it would seem, only the human species. It is difficult to detect cognitive impairment in species in the wild as survival is at such risk, but there is now an expanding literature on dementia in companion animals. So it might seem that whoever we are, if we live long enough, we dement, and that dementia is inevitable. In a trivial sense it is inevitable that as we age we acquire genetic and metabolic deficits and, as our function declines, no organ system is spared. The reality is, of course, much more nuanced.

An important point is that dementia is a syndrome, ie a running together of features that may or may not relate to a specific underlying disease process. The term dementia is somewhat imprecise and has changed over the years. Essentially, however, it refers to a generalised impairment of cognition. Until recently, an impairment of episodic memory or ability to recall day-to-day events was an essential component, reflecting in part the salience of memory in Alzheimer's disease, one of the commonest causes of dementia. Some earlier definitions of dementia, such as that of the Royal College of Physicians, referred to a global impairment. This is unhelpful as “global” implies a general and undifferentiated impairment of cognition which is far from the truth. Although now dementia is, in my view an unhelpful term, apart from raising awareness, it has in the past been very useful. Prior to brain imaging, a generalised deficit made a local, potential surgically amenable lesion much less likely. Unfortunately, the term is often misused and conflated with Alzheimer's disease, one of the commoner causes of dementia, i.e. a category error between disease and syndrome. Although dementia as a syndrome is strongly associated with advanced age, the potential distinction between old age *per se* and other specific causes was recognised early. Pythagoras referred to all of us reaching imbecility and infancy by the age of 80[ii], and Hippocrates took the view that senility and dementia were very closely linked and referred to this as *morosis*, or becoming like a child. Posidonius, however, may be the first to have separated a decline in old age (leros*)* from dementia due to other causes (morosis*)*[iii].

The view that there may be many causes of dementia other than old age gradually took hold and by 1845 Esquirol’s Treatise on Mental Derangement[iv] described a number of different causes, many of which would be recognised today. However, the major advance came in 1907 with a case report by Alzheimer of “a peculiar disease of the cerebral cortex”[v]. He had seen a patient in Frankfurt Hospital, Auguste Dieter, born in 1850, who by the age of 50 had developed memory problems and delusions of her husband's infidelity. She was admitted to the Frankfurt Institute for the Mentally Ill and Epileptic and seen by Alzheimer. She died five years later, by which time Alzheimer had moved to Munich to work under Kraepelin but arranged for the brain to be transferred. Alzheimer was able to use the newly developed stains, available as a product of the

burgeoning German dye industry and used so successfully by Nissl, to visualise brain changes at a neuronal level. In so doing, he was able to identify the two features that now characterise the eponymous disease, namely senile plaques and neurofibrillary tangles. The former are extracellular deposits of an amyloid protein referred to as Aβ. It belongs to a class of proteins that have a propensity to misfold to form characteristic beta pleats and thus become insoluble and lose function. Neurofibrillary tangles are intracellular and comprise misfolded tau protein, an essential component of the microtubule complex that provides the internal skeleton of neurons. Alzheimer's patient was young and, until well into the 1980s, Alzheimer's disease was considered to be a rare pre-senile dementia (retirement age of 65 years being the conventional cut off between pre-senile and senile). Senile dementia was considered to be separate from Alzheimer's disease and more likely to be due to vascular diseases. However, the pioneering work of Roth and colleagues in Newcastle demonstrated the frequency of plaques and tangles in so called senile dementia, albeit often in association with vascular disease. The study of younger patients avoids the comorbidities seen in the older person and allows for study of a relatively pure form of Alzheimer's disease. This is particularly true of a very rare hereditary form that is inherited as an autosomal dominant disease, i.e. there is a 50% probability of offspring being affected. The study of such families identified that the culprit genes are either directly or indirectly involved in the synthesis or breakdown of the amyloid protein that is deposited in senile plaques. This has led to the development of numerous drugs targeting the amyloid pathway and more recently the downstream tau pathology of neurofibrillary tangle formation. This does of course assume that the features of familial Alzheimer's disease can be generalised to the much more common sporadic disorder. The study of familial Alzheimer's disease also provides an opportunity to track the progression of the disease from the pre-manifest stage, something that is difficult to undertake in the general population. Such studies have demonstrated a long period where structural changes with brain tissue loss can be seen years before symptoms emerge[vi]. This is similar to the pre-manifest period of cancers that may be developing for many years before the declaration of symptoms, and early recognition may provide a window of opportunity to intervene if we do develop effective treatments. These studies show the predilection of the disease for the hippocampus and other medial temporal lobe structures involved in our ability to form and maintain memories for everyday events. This memory loss is a characteristic feature of the disease, but to focus on this alone risks ignoring other presentations due to the disease selectively picking off specialised neural networks. These other examples also provide further illustration of the danger of thinking in terms of the dementias as global deficits. Alzheimer's disease can start at the back of the brain, in the areas involved with visual processing, and can lead to a variety of symptoms relating to the perceptions of space and location. A striking example is the inability to locate an object in space[vii]. In this situation, people are unable to reach for static objects such as a knife and fork. However, far from being a global deficit of vision, the pathways involved in motion perception are spared by the disease allowing correct perception and location of a moving object.

The focus on what we can easily measure - lists of numbers, names of objects, counting, where an object is - can miss so much, not least creativity that can emerge even as some cognitive skills are lost. William Utermohlen was a portrait artist who moved from Philadelphia to London. Sadly, in the early 1990s, he developed memory impairment and with a diagnosis of Alzheimer's disease, was entered into a drug trial that we were running at Queen Square. William had ceased to paint, but with encouragement from our research nurse, Ron Isaacs, he started again and continued with a series of self portraits as the disease progressed[viii].

We have focused on Alzheimer's disease as being the commonest of the dementias, but the number of diseases potentially causing a dementia syndrome is legion and impossible to encompass in a single lecture. I would like to mention one other disease, namely semantic dementia. There is a large group of degenerative dementias that have been distinguished clinically from Alzheimer's disease on the basis of a more frontal involvement of the brain with features that involve behaviour changes and/or speech and language impairment[ix]. One such is the so-called semantic dementia. This derives from an important distinction between our episodic memory, ie our memory for events or episodes in our life, the type of memory that is so commonly impaired in Alzheimer's disease and which we tend to associate with the term dementia. However, there is also semantic memory that is our memory for world knowledge, concepts, facts and ideas. I rely on my episodic memory to recall that I came to Barnard's Inn Hall to give a lecture, but rely on my semantic memory to recall what giving a lecture means. In passing one should mention that I have given two examples here of distinct types of memory but there are many other types of memory that can be selectively spared or damaged in brain diseases. For example, short term memory needed to recall a telephone number long enough to dial is relatively spared in Alzheimer's disease.

Before returning to the question of whether dementia is inevitable and what do we do about it, I want to make the case for forgetfulness, which does have a very bad press. We are always complaining about memory but none of us can remember all details of our lives, nor indeed all the facts that confront our semantic memory. Increasingly, it is recognised that forgetting is an important part of adaptive plasticity and there is interest in how the normal physiology of forgetting may interact with disease[x]. The Argentinian writer Jorge Borges describes in Funes the Memorious[xi] a man who has total recall after a fall from a horse. It is a life impossible to lead.

So some forgetting is inevitable - indeed essential. But is dementia inevitable? The answer to this, other than in the trivial sense that if we live long enough, everything declines, is a confident No. There has been increasing interest in the study of centenarians. One famous case is that of Jeanne Calment, who died in 1997 at the age of 122[xii]. Sadly, she outlived her daughter and her only grandson, who died young in a road traffic accident. At the age of 90, she entered into a viager agreement with a local attorney, whereby he owned her apartment but on the basis that she had the right to live there and received two and a half thousand francs per month. The attorney also predeceased her. In her recent years, she underwent a CT scan and some simple cognitive tests which, allowing for her loss of sight and hearing, showed relative preservation. Importantly, there are examples of individuals continuing with excellent cognitive skills late into life. Picasso and Grandma Moses as artists, and Arthur Rubinstein as musician. It is not only in the creative arts, but also in science where there are examples. Namely, Hans Kosterlitz discovering the enkephalins when he was in his 70s.

So where are we now with treatment, and most importantly, prevention? When thinking of dementia treatments, there is a tendency to focus on Alzheimer's disease, and there have been breakthrough claims for treatments that are focused on the amyloid protein. It is very early days, but I am confident that we will have a menu of drugs that can target different aspects of the protein pathways, including, for example, tau antisense oligonucleotides. However, we need to be very careful about the use of the term “cure” as freedom from a disease is relatively uncommon, and most diseases are managed as long term illnesses, for example diabetes and many cancers. It is likely that we will move to a situation of managing the protein burden that can arise from Alzheimer's disease rather than curing, and in this situation, early intervention will be key. This view, however, assumes we are dealing with a discrete disease entity.

Occam’s (Ockham) Razor, or the principle of parsimony, is a major tool in the diagnostic process. But as we age and accumulate errors in our biology, Hickam’s dictum (a patient can have as many diseases as they darn well want) becomes more useful. A unitary diagnosis of Alzheimer's disease works very well in the young person with an APP gene mutation, but not so well in an 80 year old where the changes of AD are usually occurring together with vascular changes. Moreover, we increasingly recognise that as Alzheimer's disease advances, the abnormal deposition of amyloid and tau seed the abnormal deposition of other proteins. For example, the synuclein that is the hallmark of Parkinson's disease.

Given this complexity, prevention becomes increasingly important. A Lancet Commission led by colleagues at UCL has synthesised the evidence for potentially reversible factors, many of which are also important for preventing cardiovascular disease[xiii]. Indeed, there is evidence that the incidence of dementia in Europe and the U.S. is decreasing. This is almost certainly due to the better management of vascular risk factors, particularly hypertension in midlife. However, although the incidence may be decreasing, with increased longevity, the prevalence is still rising. The focus of the Commission is on all-cause dementia, but it is worth bearing in mind that dementia is only the tip of the iceberg of cognitive impairment[xiv]. We need to consider the challenge of maximising cognitive potential at the individual and societal level and throughout life, rather than just focus on late life dementia. Many of the challenges are wicked problems, but some lifestyle factors are manageable by each of us at a personal level. For example, exercise for both the body and the brain. Intellectual stimulation is very important, and so keep attending Gresham lectures.

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