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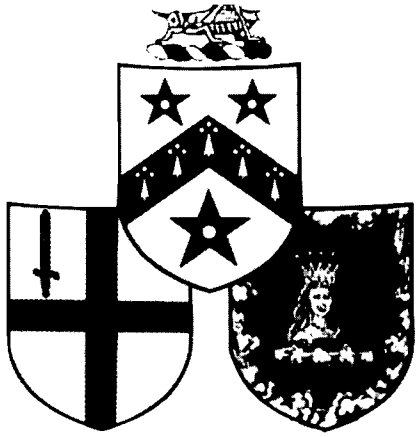

# EXPLORING THE BRAIN

Lecture 14

## ALZHEIMER'S DISEASE

by

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## Alzheimer's Disease

In 1907 Alois Alzheimer published a report on the brain of a fifty-one year old woman who had initially attracted attention because of a seemingly excessive jealousy of her husband; however this perhaps explicable behaviour had then deteriorated to more conspicuous and unambiguous thought problems now recognised as 'dementia'. Dementia is a very wide-ranging term covering memory and learning impairments, loss of intellectual functions and an overall disorientation where the patient does not know where they are. Between 20% and 40% of people with dementia are subsequently diagnosed as having Alzheimer's disease. Other causes of dementia are progressive supranuclear palsy and dementia pugilistica (caused by repeated blows to the head while fighting). Four million Americans now suffer from this devastating condition: since it is age related, the prevalence will have increased by five fold by the next century if there is no significant advance made fairly soon.

A enormous clue to the cause of Alzheimer's disease has been the abnormal change in the way the brain tissue looks when it is examined after the patient's death. Alzheimer noticed that there was a loss of cells in the upper layers of the cortex and changes in the supporting glial cells. In addition there was an accumulation of fibrous bundles and 'deposits of a peculiar substance'. The accumulation of fibrous bundles is now referred to as neurofibiliary tangles whilst the 'peculiar substance' is known as senile plaques. These plaques and tangles are the established histological hallmark of an Alzheimer brain.

Neurofibliary tangles are never found in normal aged brains, but are present in the brains of demented patients who nonetheless do not have Alzheimer's disease specifically. Neurofibriliary tangles consist of filaments some ten microns in diameter wound in a paired helical arrangement. At the core of each filament is a protein normally associated with the formation of microtubules: this protein is 'tau-protein'. In normal aged brains, the tangles are never seen, and tau protein binds to microtubules, which are normally found only in axons, to increase their stability. However, in Alzheimer's disease, for reasons as yet unknown, the tau protein acquires too many phosphates, it becomes 'hyper-phosphorylated'. In turn this hyper-

phosphorylation leads to the formation of tangles. Moreover, in Alzheimer's disease, unlike the normal situation, tau proetin is found in the somato/dendritic region as well as in axons.

It is not yet known whether the deposition of tangles is a cause or an effect of dementia. One hypothesis as to how tangles are formed is that excessive calcium entry into neurons might be a trigger. It has been shown in experiments that if calcium entry into neurons is deliberately enhanced, by stimulating NMDA receptors with glutamate, then changes characteristic of tangle formation occur. Interestingly enough, tangles are most usually found in brain regions associated with learning and memory, such as the hippocampus. It is possible therefore that in these regions, where there is the most scope for neuronal adaption, that calcium entry can go most easily awry. An abnormal, excessive degree of calcium entry into the dendrites and soma, produced by stimulation of the receiving NMDA receptors, would lead to hyperphosphorylation of Tau at its site of production, in the soma. This phenomenon would account for the presence of tangles in the soma and dendrites, where normal microtubules are usually absent.

Yet another idea is associated with a protein, apolipoprotein E (APO-E), which usually plays a role in maintaining the plasma membrane. If APO-E were in some way defective it would fail to bind to its receptor and perform its normal function in the turnover of membrane lipids. Rather, it might lead to the aggregation of tangles. Excess APO-E could be formed when degenerating nerve terminals are engulfed by glial cells. Hence tangle formation, triggered by APO-E, might occur increasingly as neuronal degeneration takes place.

Plaques differ from tangles in that they are found outside neurons: they are fairly conspicuous, being some fifteen to a hundred microns in diameter. The two basic constituents are a central core surrounded by abnormal nerve processes, dystrophic neurites. The central core consists of a protein made up of about forty amino acids and known by a variety of names: A4 protein, beta A4 protein, amyloid beta peptide, and beta amyloid. Beta amyloid is formed from the cleavage of a larger protein, amyloid precursor protein (APP), which is present in normal nervous tissue. It was once thought that the production of beta amyloid from APP was due to abnormal cleavage of the protein, which would result in the formation of plaques and might henceforth be the trigger for neuronal degeneration.

More recently it was discovered however that beta amyloid is secreted from the normal brain, and can be measured in CSF. Hence it is more likely that normally, both non-amyloid peptides as well as beta amyloid can be secreted. It might be the case then that plaques result more from a quantitative rather than a qualitative difference with the normal brain. It could be that it is not so much that any soluble, secreted beta amyloid in itself will lead to the formation of plaques, but rather that an abnormal type or a particularly high amount might do so. Alternatively, there could be an abnormal dominance of amyloid processing over the otherwise normal production of non-amyloid products.

An alternative idea is that again, excess APO-E, such as might occur during neuronal degeneration, combines with the secreted, soluble beta amyloid to form the plaques. Were this the case, we could again see that the formation of plaques, as with tangles, might be a result of a degeneration already stated and now promoted in a vicious circle, feedforward mechanism.

Although no one as yet knows the relation of plaque formation to cell death, it seems unlikely to be the primary cause. Beta amyloid is present in the cortex of some elderly people who do not suffer from dementia and where there is no cell loss; most importantly of all however, beta amyloid is often present in the cerebellum, which is a region that does not degenerate in Alzheimer's disease. Even in the case of dementia, there is a poor correlation between the degree of amyloid deposition and the degree of dementia. Hence it is possible that instead the crucial step in cell damage involves the action of the soluble, secreted beta amyloid, whereas the subsequent formation of insoluble plaques might just reflect the fate of the protein, as well as other variable factors such as the degree of APO-E present.

However we do not know the actual relation of the secreted, soluble beta amyloid to Alzheimer degeneration. If large aggregates of beta amyloid are injected into the cortex or hippocampus of rats, then neuronal loss in these regions occurs within four weeks. But then again, it seems that the protein does not work in a simple way on its own. We saw in the previous section that excessive amounts of glutamate can act as 'excitotoxins'. In such cases, beta amyloid can increase the toxicity of glutamate, even in doses when on its own the transmitter would not have been toxic at all. Moreover, the toxicity of beta amyloid itself can be enhanced by the agent needed for normal cell survival, nerve growth factor (NGF). This observation again suggests that degeneration

in Alzheimer's disease might be in some way linked to abnormal neuronal development, or that again, mechanisms such as calcium entry are beneficial in moderation, but harmful in excess.

A small number of cases (less than 1%) of Alzheimer's disease, where the disease has an early onset, are genetic in origin: 'Familial Alzheimer's Disease (FAD)'. Interestingly enough, the FAD gene is also located on the same chromososme (Chromosome 21), as the gene for APP, but the two are not identical. In other families, a gene has been located on Chromosome 19, which encodes for APO-E, which we have seen plays an important part in neuronal pathology.

The condition of stress triggers in the brain a cascade of mechanisms that in our primeval incarnation would have been powerful aids to survival. One of these mechanisms results in the secretion of a steroid hormone into the blood stream which blocks the use of glucose by most of the body tissue, so that energy is diverted to muscles, enabling us, as still primitive beings, to run away or fight efficiently. This same hormone, glucocorticoid, will also suppress the relatively luxurious pastimes of growth, reproduction and immune responses. Hence the idea that yet one of the many effects of stress in our modern lives is to make us more susceptible to illness. We have already seen glucocorticoid at work in neuronal adaptation: but what could this hormone have to do with Alzheimer's disease?

It appears that at least in rats, glucocorticoids can lead to damage of the hippocampus, which is known to display damage in Alzheimer's disease. Experiments have shown that in themselves the hormones do not kill off the neurons, but rather they make damage in response to other factors more likely. Because of the disruption caused in glucose transport, the neurons become that much more vulnerable. Hence, if a further event takes place, for example excess calcium entry leading to excitotoxicity, then the consequences will be more dire than if the corticosteroid had been absent.

Of particular significance to Alzheimer's disease, which is primarily a disease of old age, is the observation that aged rats display a high level of glucocorticoid secretion: however if secretion of the hormone is irreversibly prevented when the rats are 'middle-aged', then events which otherwise would have led to damage of the hippocampus and accompanying impairments in problem solving and learning, no longer occur. In a sense, the corticosteroid is

acting as a malevolent form of neuromodulation. If, in this way, glucocorticoid is one further factor, as opposed to the single cause of Alzheimer's disease, it would explain why not all brain regions are sensitive to damage by the hormones. Moreover, once more there is a non-exclusive use of a single substance, this time glucocorticoid, for the different but related processes of adaptation and death.

The onset of Alzheimer's disease is usually characterized by late age of onset, but the actual issue might not be so much calendar age as the fact that as we get older, our reproductive power wanes. The sex steroids testosterone and oestrogen seem to have equal and opposing action on the cells. If the sex steroids get out of hand, the cell grows abnormally, and if the corticosteroids start to outnumber their sex counterparts (as in old age) then, as we have seen in the previous section, the neurons become severely compromised. It would follow therefore that sex hormone treatment might be helpful in protecting against Alzheimer's neurodegeneration. In middle-aged mice at least, administration of agents promoting androgens or oestrogens (male and female hormones respectively), leads to improved memory retention.

As in Parkinson's disease, free radicals are frequently at the heart of the final process of cell loss: the same holds true for Alzheimer's disease also. If the neurons undergo a period of oxygen deprivation, for example as a result of a minor stroke in a sensitive and vulnerable region, then free radicals are generated within the neuron. Not only does this cause direct damage, but lack of oxygen also causes the accumulation of an acid (lactic acid) within the cell. This change in acidity levels can have a dramatic effect on chemical reactions. Some substances that were previously inert suddenly become active under acidic conditions. For example iron can become more easily liberated within the neuron, from its normal imprisoned existence with chelators such as those discussed earlier. This excess iron can then trigger the formation of even more free radicals.

Indeed iron is not the only metal that have a part to play in neuronal death in Alzheimer's disease: another metal, this time absorbed from the outside world, can also be toxic, aluminium. For whatever reason certain individuals might be more susceptible to breathing in aluminosilicates. Once internalised into the brain, these substances are highly insoluble yet will react with many other chemicals present, conceivably contributing to the appearance of some of the unusual morphological features. The big unanswered question is

still whether these unusual physical features of the cell represent the cause or effect of cell loss in Alzheimer's disease.

One problem with searching for a mechanism at the level of the single neuron, is that not all neurons in the brain are equally susceptible to necrotic degeneration. Rather, there is selectivity for destruction at the more global level of whole brain regions. Although the potential problems we have looked at so far would indeed be important in the loss of neurons in Alzheimer's disease, they cannot in themselves account for why particular brain areas are lost, and not others. Just as we concentrated on the substantia nigra for Parkinson's disease, let us look then at how Alzheimer's disease is related to the next level up, that of whole brain regions.

It seems then that Alzheimer's disease resembles that other major degenerative disease, named after Parkinson. In both cases we have seen that there is no single probable cause of cell death, but that rather a confluence of factors can conspire finally to set in train the process of death. Many of these final factors may be similar in the two diseases, for example excitotoxicity and generation of free radicals: however at the functional level, the problem presents as either a disorder of thought or as a completely different disorder of movement. The critical issue is the brain region affected.

A major region that seems to be implicated in dementia is a neuronal motorway connecting large areas of cortex with the deeper and more primitive regions of the brain involved in learning and memory: this area is the 'medial temporal lobe'. Again, damage here can occur in a variety of disorders: schizophrenia, hypoxia or amnesia. Nonetheless, in patients with dementia there is a clear correlative deterioration in this particular region that mirrors the mental decline in the disease. The size of this brain region starts to diminish as the degeneration advances. Recent studies of the progress of Alzheimer's disease, as reflected in the progressive loss of this particular region, the medial temporal lobe, reveal that Alzheimer's disease is not a generalised condition of old age.

It is possible to visualize in brains of living patients the medial temporal lobe, by means of brain scans obtained from computerized axial tomography (CAT), which operates on the same principle as the familiar technique of X-rays. The normal thickness of the medial temporal lobe in a person aged 66

years, is about 13 mm., which will slowly have diminished from some 16 mm thickness at the age of twenty years old. By contrast a patient with Alzheimer's disease may have, again at 66, a medial temporal lobe as thin as 6mm. By monitoring the change in thickness of the medial temporal lobe with age, it has been found that in Alzheimer's disease, the rate of shrinkage is far faster than in normal ageing, some 3mm per year! Alzheimer's disease then is a catastrophic event that can occur at any particular moment in later life: it is not a natural consequence of ageing.

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