The science of the mind: investigating mental health
Dementia drug research

Narrator
Professor Martin Rossor is director of the Dementia Research Centre at the Institute of Neurology at University College, London.

Professor Martin Rossor
Our research is aimed towards the pharmacological intervention for Alzheimer's disease and that really takes two forms. The first is pharmacological interventions that are symptomatic and the second, which is rather more of a challenge, are pharmacological interventions that may actually alter the progression of the disease. The easiest is that of symptomatic treatment, and the model for that has really been around interactions with neurotransmitter systems.

Work in the late 1970s and early 1980s showed that the cholinergic or the acetylcholine systems were damaged in Alzheimer's disease and these were another projection system from the base of the brain, particularly the septal nuclei to the hippocampus, and the nucleus basalis to the cerebral cortex are involved in memory systems. And so much of the interventions have been towards a cholinergic system and that's given and that's given rise to the cholinesterase inhibitors such as Donepezil, rivastigmine and galantamine the mainstay of current pharmacological treatments. It is clear though that these may have a symptomatic benefit and in trials do show that there is some benefit in a proportion of people in memory performance. There's no evidence however, nor would we expect it to affect the underlying neuro-degeneration. For that we need to look in other directions, and what we've learnt about the underlying cause of cell loss. It's been known since Alzheimer's day that the key histo-pathological features that one can see under the microscope are the amyloid plaque and the neuro-fibrillary tangle. The neuro-fibrillary tangle reflects the damage to the intracellular cytoskeleton, tau, the micro tubular associated protein is important for maintaining the structural integrity of neurons, and we know that in Alzheimer's disease that breaks down and one can see the clumping of tau as neuro-fibrillary tangles, that's one important area of research to try and stop the underlying neuro-degeneration. Recently however most attention has been directed towards the amyloid plaque and amyloid formation, and that's where much of our own interest has been directed.

Narrator
Why has amyloid attracted so much attention?

Professor Martin Rossor
That's really come about from the studies of familial Alzheimer's disease. This is rare but has been a very important model, and it was discovered around 1990 that patients with mutations in the amyloid pre-cursor protein gene gave rise to inherited Alzheimer's disease that looked clinically and neuro-pathologically very similar to the more common Sporadic Alzheimer's disease. Shortly after, mutations in the presenilian genes 1 and 2 were also found to be associated with Alzheimer's disease and it was discovered that presenilians are important in the gamma-secretase enzyme which is involved in the metabolism of the amyloid precursor protein to give rise to amyloid, and we now know that the amyloid protein, which is normally 40 amino acids long, and is a soluble protein, is aberrantly processed in Alzheimer's disease to provide a slightly longer molecule of around 42 amino acids, which then has a particular predisposition to fold abnormally, to become insoluble. We don't quite know whether the amyloid plaque is merely an end stage that has little relevance to Alzheimer's disease, whether it's toxic itself or whether, as is now thought, there's an early stage of oligo formation which is the toxic component that affects neurons. Either way a lot of attention has been

directed towards amyloid, and that's been driven also by transgenic mouse models where the mutations in the amyloid precursor protein gene and the presenilian gene give rise to a reasonably good animal model of the disease.

Narrator
The work on amyloids has led to an important discovery.

Professor Martin Rossor
In terms of research the most exciting area has arisen from these transgenic mouse models, and the discovery that immunising such mice, such as they produce antibodies to the abnormal amyloid protein, can attenuate the neuropathology, and can also ameliorate some of the clinical deficits as far as you can assess those in mice. This work has been led by the pharmaceutical industry and following the early studies of active immunisation in humans has now moved towards a passive immunisation. The early studies were halted because of the development of encephalitis, and the current studies use monoclonal antibodies against the amyloid protein, and these are in progress. A study published in Lancet Neurology had demonstrated that using monoclonal antibodies it was possible to show a reduction in the amyloid protein in patients with Alzheimer's disease using positron emission tomography with the Pittsburgh compound B-ligand, which directly lights up amyloid deposition.

The Pittsburgh B compound is named because it was developed at Pittsburgh University, and there's been almost a Holy Grail in the Alzheimer field to try and develop an imaging modality that can directly show an image of deposition of amyloid in the brain, and this was a development of a chemical that can cross the blood brain barrier and bind directly to amyloid deposits.

We've been involved in this area of work linking in with industry, but we've also been interested in exploring other areas of amyloid deposition and how one might prevent that. One lead has been from systemic amyloidoses, i.e. those proteins that are not the same as the beta-amyloids in Alzheimer's disease, but are amyloid proteins deposited in liver, spleen, and a variety of disorders referred to as the hereditary amyloidoses, and our colleague Professor Mark Peppis, also at UCL, has developed a compound that binds with sero-amyloid protein, which is produced in the liver, and binds and stabilises amyloid deposits. The particular drug that's developed, mops up SAP, and is hoped it may therefore help either to disaggregate or to prevent the formation of amyloid deposits, and we're hoping to look at this following a preliminary proof of concept study to see if this also will help Alzheimer patients. One might ask why is this of such value? Well it's the first time that scientists are beginning to get a handle on the underlying neuro-degeneration.

Narrator
But there's still a long way to go.

Professor Martin Rossor
It's going to be very difficult, I think, to find a cure for Alzheimer's disease, but it may be important in terms of preventing deterioration, and thus a direction of research is to try and diagnose early, when somebody might be beginning a neuro-degenerative disorder. There's always going to be limitations in pharmacological treatments. We have an array of drugs that may help the symptomatic treatment, but if we're going to stop neuro-degeneration we're going to need to start early, we're going to need to understand the molecular processes that lead to nerve cell death, and to try and to prevent that. And so there's inevitably going to be a limitation if we think in terms of cure and somehow rebuilding the brain once the damage has occurred. And there's also major issues around trialling new drugs.

First of all one needs to have good theoretical evidence, usually built on cellular models in the first instance, and then on animal models that one's got a drug that's going to work. But one needs early proof of concept studies before then rolling this out into the diseased population and into a broader general population of patients who have the disorder. Drug trials are now controlled by European legislation, so called good clinical practice which ensures, most importantly, the protection of individual patients who are undergoing the study, but also the integrity of the research data, so that when a, a drug is formally approved everybody can be

absolutely confident that the drug does what it says it does, and that the data on which that's based are secure and genuine. And of course this takes a very long time. There's ~~more,~~ an enormous number of different potential drugs that will be explored at the cellular level, and only a few of those may look promising. Then one has to demonstrate that they're safe, and the side effect profile is acceptable, and a lot of the early work on this may then come to nothing if the side effect profile in humans, and particularly in the population that the drug's going to be used on, is not acceptable, and sometimes that takes a long time as one begins to discover rare, but potentially very dangerous, side effects may only be after a number of trials have already taken place.

I've said that an early diagnosis of Alzheimer's disease is important and perhaps I ought to clarify that further. It's very important as a clinician that one can make a specific diagnosis of the cause of cognitive impairment, or the cause of dementia. It's only too easy to assume that a patient is either suffering from vascular dementia or Alzheimer's disease, which are the two most common. There are many causes of dementia, some of which are in fact treatable, and so a precise diagnosis is important. Do we need an early diagnosis of Alzheimer's disease? Well where we are at the moment I think this raises a number of issues, some of which are ethical. Do we want to make a very early diagnosis if there's nothing that can be done? That's always difficult if you're in a situation where research is ongoing and there's a prospect of treatment in the future. Many patients know that they are at risk and some choose to undergo pre-manifest or pre-symptomatic genetic testing, and they make that choice that they want to know what the future holds. So early diagnosis is a partnership between the patient and the doctor. If somebody wants to know what is going to happen to them and asks the doctor if they can advise to the best of their ability, then I think that's what should be done. But as we move towards treatments, and that includes the whole panoply, including psycho-social treatments, if you have a diagnosis you know how to help, so for that reason I think there's going to be an increasing pressure towards early specific diagnosis of anybody with early cognitive impairment.

We also need to recognise that Alzheimer's disease is particularly common in old age when there are many other comorbidities. We can't at 80 run as fast as we could at 20, and we can't expect that we're going to have the same cognitive abilities and speed as we get older. But I do think that we can help with the symptoms with a variety of pharmacological interventions, and I do believe that as we understand the reasons for the neuro-degeneration, then we will develop drugs that can help to ameliorate and to slow that. They're going to have the greatest impact in younger patients where there are not other comorbidities. This does not mean to say, though, that this is the answer to Alzheimer's disease, or to other causes of dementia. Management of patients, whatever the disease, is always multidisciplinary, it always requires many different approaches, and a psycho-social approach is, of course, equally important as the biological interventions.