I apologise for not speaking to you in your own language, but you will understand my English better than you will understand my French. It is wonderful to come to Paris, which is a beautiful city and you are privileged to have a capital like Paris, which is also the home of chlorpromazine in St Anne’s Hospital here. I will talk to you this morning about the relationship between vascular disease, depression and cognitive impairment.

First of all, I will speak about depression. In my country, we specialise in older people and have done a lot of epidemiological work across the whole of Europe, looking at the amount of depression in the community. Generally speaking, in hospitals, the prevalence of depression is quite high. However, if you look at older people in Paris over the age of 65, you will find that something like 11% will have depression in the community and these people will require help for the treatment of their depression. It is therefore a big problem.

Since the early 1960s, it has been noted that there are some people with depression who have cognitive impairment and you will be familiar with the terms ‘pseudodementia’ and ‘reversible dementias’ of depression. In 1962, Felix Post, identified and talked about two types of depression in older people: depression that comes on late, for the first time in the sixties and seventies; and depression that somebody has had off and on throughout their lives.

The idea that there are two types of depression has been exemplified and illustrated in many studies. I will use just one study to illustrate my point. If you take people who have depression in their adulthood and mature into their old age, they are likely to have a family history of depression, personality issues which contribute to the depression and stress - life events; contributing to the depression. However, if you take depression that comes on for the first time in late life, very few of these characteristics are usual and often the depression is associated with vascular disease.

I want to look now at the relationship between vascular disease and depression. Firstly, I will be looking at the relationship between heart disease and depression and peripheral vascular disease and depression. I will then look at cerebral vascular disease and depression.

Let us first look at the links between vascular disease and depression, particularly peripheral vascular disease and cardiac disease. Firstly, we know that in depressed people there is an increased likelihood of myocardial infarction. Therefore, when you have an old man and an old woman and the old woman dies, it is a strong possibility that partner will die from “a broken heart”. The evidence is there. When you are dealing with bereaved people, they are likely to die from myocardial infarction related to depression and stress associated with the bereavement. This has been shown in a wide variety of studies, of which I have listed just a few.

I want now to look at depression causing vascular disease. There are many studies of community populations, depressed in-patients, the very old and patients in rehabilitation demonstrating that depressive illness is associated with vascular disease. Why is this? Perhaps it is mediated through the endocrine system and hypocortisolemia. However, there is no doubt that from an epidemiological point of view, there is a relationship between depression...
being a risk factor for heart disease and heart disease - vascular disease - being a risk factor for depression. This is so much so that in recent reviews, the link between depression and vascular disease is so close that Hamos, Vincent et al suggest that they have a common pathophysiological pathway, perhaps, again, through the endocrine system.

I will now move on to look at cerebrovascular disease and depression. Firstly, I want to look at transient ischemic attacks, stroke disease and depression and I understand that there is major work in stroke disease and depression here in Paris. We know that transient ischemic attacks are small attacks of ischemia to the brain, with no residual symptoms, and are associated with subsequent depression. We also know that in perhaps 30% of people, who have had a stroke, will experience depression and in some studies, depression has been particularly associated with the frontal lobe pathology. This is important and we will revisit this later in my talk. However, there are studies which conflate and disagree with this and suggest that perhaps the stroke and the depression are linked to systemic and cognitive impairment rather than a particular lesion in the frontal lobe. Interestingly enough, there is an increased risk of depression when you have a silent stroke - a stroke where there is no manifestation of cognitive motor or sensory deficit. The ambiguity regarding this research is still evident and people are still researching the relationship between frontal lobe stroke and depression.

My next step is to look at the relationship between vascular dementia and depression. There are a variety of studies that we can look at from an epidemiological perspective to explore this. We can look at cross-sectional studies, short-term and long-term population studies. If we look at cross-sectional studies, some of which have been done here in France, there is clear evidence that there is a relationship between vascular dementia and depression. It is a very strong relationship. If we look at the shorter follow-up studies - the longitudinal studies - there also appears to be a relationship, particularly, for example, in people presenting to memory clinics where they are being prescribed acetylcholinesterase inhibitors for dementia. They present with depression and some cognitive impairment - some memory loss. They are treated with antidepressants and they get better. However, in follow up, they begin to deteriorate.

Nevertheless, it is particularly interesting when we look at very long-term studies. If you start off at three years, depression did not predict future cognitive impairment. At four years, perhaps it did in women. In a large study of five years, depression predicted not vascular dementia but Alzheimer’s Disease. At eight years, it predicted dementia, but the people had to have hypertension - high blood pressure. Two studies of 12 years showed that there was really no relationship between depression and long-term development of dementia. Therefore, the longer the study, it seems to me, the less the association between depression and dementia, leaving considerable ambiguity concerning this matter in terms of epidemiological studies.

Let us summarise the situation so far with regard to the epidemiological studies then. Most cross-sectional studies will, of course, show this relationship between depression and dementia and most clinical studies will also show this relationship. However, the longer-term, population studies are ambivalent in showing the relationship between depression and dementia.

I will now leave the epidemiological studies and move forward to the clinical studies looking at the relationship between vascular disease and depression. Since the early 1960s and 1970s, we know with computerised tomography (CT) scanning at the Maudsley, that Jacobi and Levi found cerebral atrophy in older people who are presenting for the first time with depression. Subsequently, in the early studies, using magnetic resonance imaging (MRI), they found white matter lesions and deep grey matter lesions in the brain, associated with new onset depression in older people. These findings have been further emphasised and demonstrated in much larger recent studies, which clearly show that there are changes in the brain associated with a subgroup of people who are experiencing depression for the first time in late age.

When we start looking at the brain in more detail and where these lesions are, there is some work which is quite precise and very elegant, principally from Newcastle, in England, and America. They have found from MRI studies that it is the front part of the brain and the deep matters between the basal ganglia and the striatum and the brain which is affected by vascular lesions in people with depression coming on for the first time in late age. These MRI studies have been supported by functional studies, using electroencephalography (EEG) and single photon emission computerised tomography (SPECT) and positron emission tomography (PET) scans, where they are looking at the function of the brain in these people with depression and are finding that the function of the front part of the brain is affected.

I would like to ask you a question. Is there a case? Have we the proof for vascular depression? I would suggest that the case is building and that there is a lot of evidence that is exciting. We know that there is epidemiological evidence showing the relationship between cardiovascular disease, peripheral disease and depression. We know that depression is associated with transient ischemic attacks and stroke disease and we know that there is possibly a relationship between depression and dementia. We also know from clinical studies that depressed people are more likely to have frontostriatal damage due to vascular disease. I would argue that the evidence suggests that vascular depression, coming on late in life, is a real clinical entity that has implications for our clinical practice, for the prognosis of the patient, and for the treatment and diagnosis. That is what I hope in the last part of my talk to describe to you.

When we are describing vascular depression, we have to accept - using this model - that there are lesions in the front part of the brain. Consequently, our patients with vascular depression will present with frontal signs. In essence, this means executive dysfunction. Executive dysfunction, described by Reynolds, is the process of organisation of thought in order to execute appropriate behaviour. Therefore, if somebody with vascular depression is present-
ing, we can expect problems with executive function. The psychologists amongst us and those people used to working with older people will be familiar with a lot of the tests that can be used to explore executive function and related cognition. Indeed, in the early 1980s, Alexopoulos, in America, started to typify vascular depression from a clinical perspective and more recently described the clinical characteristics of somebody presenting with vascular depression. Fundamentally, we must look for risks of vascular problems - transient ischemic attacks, hypercholesterolemia, hypertension, evidence of stroke disease and neurological testing to show changes in reflexes. We might have to do MRI scans. Alexopoulos decided to take the age of 65 and say that people over the age of 65 are more likely to have this problem. This is interesting, because I understand the age of 65 emanates from Bismarck, and is to do with retirement when first introduced into society, and has very little to do with science and epidemiology. Indeed, I would argue that somebody could present with vascular depression under the age of 65 quite easily.

There are ‘supportive’ clinical characteristics of vascular depression. In particular, we have psychomotor retardation presenting in the older person, which is often associated with agitation and limited depressive ideation. These people do not feel depressed; they feel ill. One third of people over the age of 65, who are suffering from major depressive disorder, will deny the feeling of depression if they are asked whether they are depressed. They will say that they feel ill. Therefore, when you give them an antidepressant, they will it. They want treatment for their disease, not some weird depression they do not think they have. They are more likely to be disabled and we have an absence of family history. Interestingly enough, this concept of vascular depression has been taken into the concept of bipolar affective disorder by Steffens and Krishnan. Their criteria are similar to that of Alexopoulos, although you will see that they have arbitrarily taken the age of 50, as opposed to 65. Perhaps we need to look at the validity of including age as a criterion most importantly, the increased disability is very evident in these people.

Let us look at the implications for treatment. There has been some research, mainly based in the context of randomised controlled trials, where they have looked at the outcome of vascular depression treated with antidepressants and you will see that the prognosis is not good. Not only are vascular lesions associated with poor outcome, but also executive dysfunction is associated with poor outcome. However, our glass is not half empty; it is half full. We have some good news. If we treat these people with psychosocial intervention, augmenting - in combination with - antidepressants, we can actually improve their quality of life and treat their condition quite well.

I will now look at a case study to demonstrate the problems that we come across. I operate in a specialist unit working with affective disorders in older people and we get referrals of people to my unit who are very difficult to treat. We undertake psychotherapeutic pharmacotherapy with these people and I would like to introduce you to Mrs Smith.

Mrs Smith is 74, years old. She has been a happy woman, with a close family and a loving husband. She is an extrovert and is a ballroom dancer, where her speciality is Latin-American dancing. She has two daughters living in London and she lives in my home town of Liverpool. The daughters are teachers and she was a teacher as well. She is intelligent and bright. She presented to us with a six month history. She had had an episode of depression in her twenties when she had her first child, but it was not really treated and she got over it.

However, I want to tell you about the current presentation. It was dramatic. I want you to imagine a clean, well-maintained house, with an extrovert, wonderful lady and her husband, living in their retirement, going out and about. They are members of the church and they go to ballroom dancing. Christmas is coming and she gets a little nervous because her daughters are going to come and visit. One day, she wakes up and says to her husband that she cannot have her daughters visiting, that it is too much. Her husband thinks this is bizarre because it was she who wanted her daughters to visit. We have a radical, acute change and in the following weeks she becomes more withdrawn. In particular, she becomes agitated, and over the next month the housework falls away. She is sitting in her chair and does not engage in eye contact with her husband or go to her ballroom dancing or to church anymore. She starts moaning and wailing and rocking in her chair. You can interrupt her and speak to her and she will speak back with one or two sentences. However, her voice is flat and there is no reactivity. Her answers are monosyllabic. She says ‘yes’ and ‘no’ and is wailing in the chair. She does not want to cry and does not describe herself as depressed. Her thoughts are preoccupied with her daughters coming and she is over-generalising and catastrophising. She is getting frightened and becoming dependent now on her husband and cannot let him go out of the house without her. Her sleep is deteriorating and her appetite is falling away and she is losing weight.

Most importantly, she has no history of vascular disease or any cardiovascular risk factors. Her general practitioner starts her on fluoxetine, but there is no effect after two months. He therefore changes it to citalopram and after another two months there is no effect. She comes to our unit and we start her on mirtazapine, titrating the dose up. She makes a little improvement and her sleep settles a little bit and she puts on a bit more weight. However, she still has the residual anxiety and the churning in her abdomen. The wailing and moaning is less and the rocking is also less. We therefore introduce citalopram with the mirtazapine. However, she is still poorly-motivated and lethargic and is not doing the housework. We therefore introduce her into rehabilitative and educational psycho-social therapy - a four to six-week group work with other depressed elderly people where we explain what the disease is and what her problems are and help her to think about her thoughts about Christmas and put them into the appropriate context. However, it is evident from early on that she is unable to think about these things. She cannot conceptualise the issues or motivate herself at home to fight her depression. We therefore take her out of the group and
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Do further investigations. We look at her conceptual thinking and aspects of the frontal lobe and we find that she has a problem that we, retrospectively, should have picked up within the group therapy. Most importantly, she has lacunar infarcts - micro infarcts - in the frontostriatal area of the brain.

We took her out of the group therapy and instituted a behavioural programme and augmented her treatment with lithium. She is now on mirtazapine, citalopram and lithium. We put her on a personalised behavioural programme, using activity scheduling, graded task assignment and operant conditioning, structuring her day and using her husband as a co-therapist to work with her at home through education and our outreach teams going into her home because she was too unable to come to the hospital. Slowly, over a period of time, we get improvement. Our behavioural programme of treatment developed into a supportive treatment, where the husband and she are working together to overcome her depression, having been discharged home. He is now taking her back to church, although they have not gone dancing yet. More importantly, she is not distressed; she feels relaxed and is speaking to her daughters, who are visiting. However, she continues suffering from motivational problems. She needs stimulation and does not have volition. As we say in Liverpool, her ‘get up and go’ has got up and gone. We therefore try to promote that with her husband and she is actually probably as well as we can get her.

Let us look at the lessons we have learned. From a diagnostic perspective, we have this acute onset, with a profound agitation. We have no evidence, at first, of cardiovascular risk factors, which are only picked up through secondary investigation. We have failure to respond and she needed heavy psychosocial and behavioural treatment. The message that I have learned here is that we need to treat these people aggressively, with combination and augmented antidepressant therapy and structured behavioural rehabilitation and long-term intensive follow up.

If you look at the future possibilities in treatment, there is some exciting research. Here in Paris, people are using transcranial magnetic stimulation (TMS) - Tarango et al - and calcium channel blockers - augmenting drugs and antidepressants, particularly problem solving therapy as augmentation and behavioural therapies, as well as structured community follow up. This seems to offer these people the best outcome.

I want to leave you with the idea that there is such a condition of vascular depression and, as clinicians, we miss it very frequently and do not think about it nearly enough for the benefit of our patients. I also want to leave you with a picture of my home city, Liverpool, the European City of Culture 2008, to which you are all welcome.

Questions and Answers

From the floor
Thank you very much for that beautiful presentation. I am very interested in your opinion on two hypotheses. Firstly, what do you think about drugs being used for the prevention of cerebral vascular diseases to reduce the risk of vascular depression? Secondly, what do you think about antidepressants that promote ischemic recovery. For example, dopamine and norepinephrine enhancing agents may be favoured in vascular depression and antidepressants that inhibit ischemic recovery apha-adrenergic-blocking agents are being avoided. Is that your opinion?

Pr WILSON
I think that the research needs to be done on the latter question in order to demonstrate its efficacy. However, theoretically, you would expect that these antidepressant agents that prevent vascular changes would be potentially useful. However, I am not familiar with any randomised controlled trials yet. Secondly, we now tend to put our patients with vascular depression on statins and aspirin in prophylactic. Again, the research evidence based is very poor.

From the floor
You spoke about post-stroke depression, but have you read about pre-stroke depression, by which I mean vascular mechanisms underlying the occurrence of later depression?

Pr WILSON
Yes. This would fit with the hypothesis, wouldn’t it, that depression will promote vascular and stroke disease. I explained that with the heart there is a two-way relationship with stroke disease and that depression can predict later stroke and transient ischemic attacks in particular. I agree. That is the case.

From the floor
I have two questions on your presentation. The first question is about dementia, especially Alzheimer’s Disease. I wonder about the relationship between the occurrence of depression in mid-life and Alzheimer’s Disease in late life. A few months ago, I think, there was a publication on this where the authors said that the occurrence of mid-life depression was a risk factor for Alzheimer’s Disease. Do you agree with that?

Pr WILSON
One of the interesting things about Alzheimer’s Disease is that when you look at the brains of people in their seventies and eighties with Alzheimer’s Disease, about half of them also have vascular change and the relationship between Alzheimer’s Disease and vascular disease in the brain is questionable. In most Alzheimer’s Diseases, you will get changes in the vascularisation of the brain and dysfunction of the small arteries in the brain. This may be as a consequence, but it may be causing Alzheimer’s Disease. The relationship would therefore fit. If you have depression throughout your life, it will be more likely that you have vascular change and if you accept that Alzheimer’s Disease is a disease of repair of the brain, you could expect that there would be a link. Epidemiologically, there seems to be a link, but the science in terms of brain pathology is not really clear yet.
From the floor
The second question is about the duration of the treatment in depression in vascular dementia. Is the duration longer?

Pr WILSON
Generally speaking, when you are treating older people with antidepressants, you are taught that in younger people an antidepressant will take some four to six weeks to work. In older people, you will get the optimum result of an antidepressant in about eight weeks, with a selective serotonin reuptake inhibitor (SSRI) in first treatment. In older people generally, therefore, the treatment is longer than in younger people. Currently, we are undertaking a randomised controlled trial, comparing sertraline, mirtazapine and placebo in the treatment of depression in people with Alzheimer's Disease. We anticipate that it will take a lot longer for them to get better because of the cognitive deficit and the changes I illustrated in my talk. I also anticipate that they are also going to be more likely to relapse. It is also possible from the work that we have done with sertraline that it will not be as effective as mirtazapine in the long term treatment of depression in this group of people.

From the floor
What about the total duration of the treatment?

Pr WILSON
In younger people, we work on the idea that a depressive episode lasts between six months and a year. Therefore, when you treat a younger person with an antidepressant, you get them better and you then keep them on the antidepressant for approximately six months in the UK. In older people, the epidemiological evidence in our European studies suggests that a third of older people will still be depressed three years later. Even in older people, therefore, you have to keep them on the drug longer and, routinely, when we get an older person with a first time depression, we will treat them for a year with the antidepressant. If it is a second occurrence, we will treat them for three to five years and if they are depressed over the age of 80, we will keep the on the antidepressant for life. The same will apply, I expect, to the dementia.

Chairman
In the discussion regarding depression and dementia, did people take into account the number of depressive episodes, especially in the longer longitudinal studies, when you say that the longer it is, the less there is a relationship between depression and dementia.

Pr WILSON
I think that a lot of their data was extracted retrospectively from case notes and I do not think that they went out and interviewed people. It was done by paper and I do not think that they have that degree of detail.