



## 1ST EUROPEAN BRAIN POLICY FORUM

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### A Focus on Parkinson's Disease and the European Society

Report prepared by Laura Spinney

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## **Introduction**

The first of a series of annual, multidisciplinary forums launched by the European Brain Council (EBC) to bring stakeholders together to discuss a major brain disease took Parkinson's disease (PD) as its theme. The goal of the forum is to highlight the imbalance between the societal and individual costs of brain disease, and the resources allocated to dealing with the problem, and to help build a coordinated European research strategy to tackle it better in future. Each forum will open with an analysis of the burden and cost of the disease in question, and will then allow patients, policymakers, scientists, doctors and industry representatives—all those with a stake in disease-related research—to have their say. Overall, the forum will take the form of several series of short presentations followed by moderated discussion periods, and a final session for conclusions and recommendations. The 2008 event was attended by about 160 people and was moderated by the former television journalist, Martyn Lewis.

## **Presentations**

**Wednesday 27 February**

**Opening address: *Martyn Lewis***

In 2004, 127 million or one in three European citizens were living with a brain disorder, at a total cost of €386 billion. Brain research received 8% of the life science budget in the European Commission (EC)'s Fifth Framework Programme of research (FP5, 1998-2002), and 10% of that budget in FP6 (2007-2010), a proportion that is likely to continue to grow.

### ***Jes Olesen***

The long-term mission of the EBC is to combat fragmentation of brain research into sub-disciplines and to encourage cooperation and collaboration. The philosophy of the EBC is in many ways the philosophy of the EC: that national interests are also European interests, and cooperation is the best way forward.

### ***Janez Potočnik***

Europe faces three major challenges in the 21<sup>st</sup> century: globalisation, an ageing population and the fragility of the environment. The three overlap in the domain of health. PD is the fourth most common nervous system disorder, with 800,000 people afflicted and 75,000 new patients diagnosed each year, in Europe. Yet the causes of PD are poorly understood.

The goals for the European Union (EU) are to prioritise research, to coordinate national and international activities, and to ensure that member states learn from one another. It is already contributing to these goals by introducing new elements into the European Research Area, such as better mobility for scientists, a means of agreeing on a common European infrastructure, an intellectual property charter and support for international cooperation beyond the EU. It is also engaged in joint programming. The model in the latter area is energy planning; health should be next.

The EC supports the EBC's goals and supports the need to increase the brain research budget. However, EC money only represents 5% of the public budget for R&D, and the public budget only represents 20% of total R&D funding in Europe. EC funding will favour those organisations that can prove they are cooperating across public and private areas, and for 60% of its budget this is already the case.

The key message is that the EC cannot drive change in a top-down manner. Recognition of the need to invest more in brain research must come from the member states, who will have to cooperate and push hard to have their case heard.

### **Keynote address**

### ***Bengt Jönsson***

There is a need for new measures of the value of medical progress, in order that decisions can be made about resource allocation for R&D, and about the levels of reimbursement for new treatments (especially as third party payment of costs is becoming increasingly important in Europe). The burden and cost of disease can be useful measures for identifying unmet needs and the potential for improvement. They can also be used to make comparisons between diseases and between countries, and they can be related to investments in prevention and treatments as a first step to assessing the cost effectiveness of such strategies.

There are two accepted measures of burden of disease: disability adjusted life years (DALY) and quality adjusted life years (QALY). The cost of disease is divided into direct and indirect costs, where the former refers to resources used within or around healthcare services, and the latter to loss of production and income. According to the World Health Organization (WHO), the total DALY lost to PD in Europe is 315,000, and the QALY 260,000. The prevalence of PD in Europe is estimated to be 1.3 million at all ages (1.16 million aged 65 and older), though there are few adequate studies of this. The total value of QALY lost is €13 billion, and the estimated loss of quality of life per patient is 0.2 (on a scale of 0 to 10).

The EBC's Cost of Disorders of the Brain in Europe (CDBE) study found the total direct cost of PD to be €10.7 billion in 2004. Of that, the biggest proportions spent outside the healthcare system go roughly equally on social services and on patients' private expenses. The two together account for 57% of the total direct cost of PD. Based on three national studies, indirect costs represent about 80% of direct costs, so it is estimated that the total indirect cost of PD in Europe is approximately €8 billion. However, the cost per patient varies across EU member states, reflecting differences in income and purchasing power. Switzerland was near the top of the league in 2004, for example, and Poland near the bottom. Hospitalisation represents 10% of the total cost of PD in Europe, drugs 14%.

It is important, also, to look at the cost per patient stratified by disease severity. Of the 1.3 million PD patients in Europe, 130,000 or 10% are estimated to have been younger than 50 at the time of diagnosis. As the disease progresses, informal care becomes more important, however this factor has not been systematically included in economic studies of PD.

More data are needed on the following economic aspects of PD: indirect costs; informal care; direct, non-medical costs (such as out-of-pocket expenses of patients and their families); utilities and quality of life; regional data (data is lacking for entire regions such as the Mediterranean and central Europe) and patient management. With regard to the latter, healthcare costs are likely to be underestimated, for example because studies predate new treatments, or because there have been no studies of the cost of diagnosing PD.

#### **Panel discussion—theme one**

***Olivier Rascol***

The recorded history of PD goes back to ancient descriptions of shaking. James Parkinson gave his name to the disease in 1817, and among the treatments proposed in the 19<sup>th</sup> century were belladonna alkaloids, by Charcot, and a vibrating helmet, by de la Tourette. In the 1950s, synthetic anticholinergic drugs and ablative surgery were among the treatment options; in the 1960s the antiviral drug amantadine was added (its beneficial properties were rediscovered more recently). Understanding that the disease was associated with a lack of dopamine finally led to the discovery of the current frontline treatment, levodopa, in 1967.

Levodopa transformed patients' lives, but it did not solve all their problems. It is now known that the PD brain is sick long before the patient shows symptoms. Once diagnosed and treated, patients experience a drug "honeymoon" when all the drugs work effectively, after which time they start to create problems of their own. In the years since levodopa was introduced, medical science has been searching for ways of dealing with those problems.

Among the most important developments have been adjunct therapies for motor complications, such as catechol-O-methyltransferase inhibitors, and subthalamic deep brain stimulation (DBS), both developed in the 1990s. The challenges for science in the 21<sup>st</sup> century, as far as PD is concerned, include neuroprotection, novel dopaminergic and non-dopaminergic medications that deal with both motor and non-motor symptoms, and novel surgical targets for DBS.

***Werner Poewe***

The diagnosis of PD is not straightforward, and studies have suggested that 25% of cases are initially misdiagnosed. PD is classified on the basis of symptoms and degeneration. Around 12 genes are known to predispose to it, but the predispositions are to different forms of PD. It cannot, therefore, be regarded as a single disease. For example, there are patients who present with tremor and never develop severe immobility, while others have much reduced mobility but no tremor; PD can cause dementia in some, while others show no cognitive deficit. The symptoms are determined partly by age of onset, with early- and late-onset disease presenting very differently. The reasons for this are not known.

In order to increase clinicians' confidence in diagnosis, we need to expand the list of diagnostic tests. Tests are becoming available which detect the disease in the preclinical phase, by looking for signs such as an impaired sense of smell, depression or subtle motor impairment. As these tests become more widespread, we need to plan treatments earlier, and to start considering preventive treatments in pre-symptomatic people.

***Peter Brown***

Though researchers now have some knowledge of the genetic and environmental causes of cell death in PD, it may be more useful to target the pathophysiological mechanisms of the disease—that is, the mechanisms linking cell death to the symptoms. Imaging and functional neurosurgery can offer insights here.

Clinical research is needed to help patients, but also to feed back into basic research. For example, abnormal neuronal activity in the basal ganglia (brain structures affected by PD) at a frequency of 20Hertz is known to be correlated with PD-related motor impairment, and in fact stimulation of the brain at 20Hz exacerbates that impairment. Having found this abnormal activity, researchers went back to one of the oldest animal models of PD, the 6-OHDA-lesioned rat, to look for it. They saw it in chronic lesioned rats, but not in un-lesioned rats that had been treated with dopamine antagonists (an acute model of the disease). It seems, therefore, that the abnormal activity takes time to develop, which in turn suggests that there may be a therapeutic window for preventive treatment.

### ***Eduardo Tolosa***

Levodopa is the best drug available for the symptomatic treatment of PD. In the last 30 years, the main developments in the treatment of the disease have been apomorphine, a dopamine receptor agonist which mimics dopamine rather than replacing it (as in the case of levodopa), and Duodopa, a form of levodopa which is delivered directly to the small intestine and which is useful in complicated or advanced cases of the disease.

We cannot yet effectively manage the disabling, non-motor symptoms of PD, such as depression, hallucinations, sleep disturbances, erectile dysfunction, hypersalivation and pain, but progress has been made and we can at least delay some of them now. It is possible, for example, to ameliorate a cognitive deficit in those with PD dementia, and hypersalivation can be treated by injection of botulinum toxin into the salivary glands.

### ***Pino Carbone***

Medtronic produces the technology for DBS, an alternative to drug therapy for a subset of PD patients. DBS, which is a descendent of the ablative surgery performed in the 1950s for PD, blocks the signals that cause the disabling motor symptoms associated with the disease. It helps patients to control their movement and leads to dramatic improvements in their reported quality of life. Among its benefits are that it is adjustable via remote control, and it is reversible; its drawbacks are mainly the risks associated with surgery, including infection.

Over 40,000 people have been treated with DBS worldwide to date, and there are 160 DBS centres in western Europe. Crucial to the success of DBS are appropriate patient selection and accurate surgical placement of the DBS leads. Today, many eligible patients are never referred for DBS and live with their symptoms

unnecessarily. In contrast, up to 63% of patients who are referred for DBS are not suitable for the operation. Neurologists therefore need better training in patient selection. Good patient follow-up is also essential.

### ***Emilio Moreno***

The diagnosis of PD is still mainly a clinical exercise, despite advances in imaging and genetics. However, the fact that around a quarter of all cases are initially misclassified, and that research has shown that early initiation of drug therapy can produce a benefit for the patient, there is clearly a need for better early diagnosis.

DaTSCAN is a radioligand used in single photo emission computed tomography (SPECT) imaging, which binds to dopamine transporters in the brain. It is useful in the diagnosis of uncertain and early cases of PD, and particularly in the differential diagnosis of PD and essential tremor. Scans without evidence of dopaminergic deficit (SWEDD) become less likely as the disease progresses. DaTSCAN is cost effective on a five-year horizon in terms of time spent on appropriate therapy, or adequately treated years. The challenge for the future will be diagnosing preclinical disease with these methods.

### ***Wolfgang Örtel***

PD experts must know how to treat the non-motor as well as the motor symptoms of the disease. The Movement Disorders Society exists to educate clinicians who work with PD patients in how to treat the whole patient (a summer school will start in 2008, for example), to promote research, improve patient care and attract a new generation of medical students to the field.

The management of PD is not driven by the movement disorder expert, but by the patient, their carer or health insurer, as well as by the media. The movement disorder expert therefore has to work within this network. It is essential that all those affected by the disease speak with one voice—particularly when it comes to accelerating patients' access to treatment, and addressing variability in the standard of care across Europe.

### ***Discussion***

Hungarian neurologist Annamária Takáts asked for more details about how the diagnosis of PD was going to change in future. Werner Poewe replied that as diagnosis moves more towards the early, preclinical phase of the disease, clinicians will have to rely on biomarkers of the disease to detect it. The reliability of those biomarkers will become a major ethical issue, as it has been in another degenerative disease, Huntington's.

The question of the traditional division of care of PD patients between neurologists and psychiatrists was raised. There was a consensus among the panel that a multidisciplinary approach to patient care was best. The neuropsychiatric dimension

of the disease was once again highlighted, and Olivier Rascol pointed out that patients can have problems involving sleep, bladder control, pain and blood pressure. Jes Olesen said that multidisciplinary clinics should be built around a single disease, in this case PD, but Eduardo Tolosa warned that this was not always possible. Mary Baker pointed to multidisciplinary clinics that already exist in Tel Aviv, Israel and Nijmegen, the Netherlands, which she said were highly cost effective, though she recognised that establishing such clinics required a colossal effort on the part of the coordinating neurologist. She said that he or she needed the support of the patients to pull it off. A patient from Tel Aviv who had been treated in such a clinic described her experience very positively.

Michael Rogers, a former ethical advisor to the EC's research Directorate-General, asked why, if the advantages of early treatment were so obvious, patients weren't receiving it. Peter Brown and Olivier Rascol both responded that while the advantages of early diagnosis were clear, the advantages of early treatment were less so, though they are being investigated. To date, the strategy has been to wait until the symptoms appear before beginning treatment, partly because of the problems associated with chronic levodopa treatment. Jes Olesen asked why it was so difficult to slow the progression of the disease. Wolfgang Örtel replied that most drugs had been developed for the treatment of symptoms, rather than to slow the underlying neurodegeneration, and that they had been developed in animal models which only approximated to the human disease. Werner Poewe added that the progression of PD was very slow, and nobody was prepared to invest in the long clinical trials that would be needed to look at the effects of early treatment on disease progression. Jose Vazquez of the EBC asked what the average interval was from a patient's first visit to his general practitioner (GP) and a definitive diagnosis. Werner Poewe said 18 months.

## **Panel discussion—theme two**

### ***Tom Isaacs***

The real shackles of PD are the pain, worry and embarrassment it causes patients, but these shackles can be avoided, for example, by thinking about others with the same condition. Communication is the strongest medicine of all, particularly communication between patients and the scientists and doctors who are working to improve their situation. Patients have an overwhelming need to understand the disease and their treatment. At the moment, however, they feel the world of science is distant from them.

### ***Suzanne Lindvall***

It has been estimated that for every person diagnosed with PD, 10 people are affected. In the fictional case of "John", those affected include John's extended family and friends, his customers, colleagues, boss, insurance company, doctor and neighbours. There are also the members of his house owners' club and the

members of the jazz band he plays in. Because people with PD are easily stressed, as are people who come into contact with them, those affected more transiently by John's condition include the cashiers and customers in the shops he patronises, the driver of the bus and taxis he uses to get around and the waitress who serves him in a restaurant (though he hates to go to restaurants, because of the difficulty he has eating). So the number of people affected for every person with PD is closer to 100.

**Wolfgang Oertel** (for Paolo Barone, University of Naples)

PD is not just a movement disorder, but a disorder of the whole body and brain. Studies suggest that 55% of patients' quality of life is driven by mood, and only 15% by movement. A neurologist treating PD must therefore know how to deal with mood disorders. The motor symptoms of PD may mask depression, a common complication of the disease. There is a tendency among clinicians to explain away the depressive symptoms as understandable reactions to PD, or to put it down to older age or dementia, but the depression associated with PD can be treated, and it is as important to treat it as to treat patients' immobility.

Profile of Depressive Symptoms in Parkinson's Disease (PRODEST-PD) is an observational, multicentre, European study involving over 1000 patients. The initial results of the study indicate that 28% of those patients have a history of depression. Could depression be an early symptom of PD? We don't know. More research is needed into the mood disorders associated with PD.

**Grzegorz Opała**

The European Parkinson's Disease Association (EPDA)'s 1997 Charter for People with Parkinson's Disease states, among other things, that patients have the right to be referred to a doctor with a special interest in PD, to receive an accurate diagnosis and to receive continuous care. Are these rights respected evenly across Europe?

The WHO's Neurology Atlas indicates that the answer is no. It also indicates that there is no clear relationship between the number of neurologists in a country and the amount it spends on parkinsonism. For example, there are more than five neurologists per 100,000 head of population in Poland, which spends almost €3000 per case of parkinsonism, and between 0.1 and 1 neurologists per 100,000 head of population in the UK, which spends closer to €10,000 per case.

The standard of care of PD patients depends on many factors, including: the number of specialists and multidisciplinary centres; reimbursement of treatment, including DBS, rehabilitation and occupational therapy; patients' associations (there are 39 in Europe) and healthcare and social services. To illustrate some of the current inconsistencies in the standard of care, the drug Duodopa is registered in all European countries, but only reimbursed in 14. DBS is available in 14 countries, but implant rates per million per year in 2006 varied from 0.6 in Poland to 18.4 in Norway. So no, there is no equal standard of care in Europe.

### ***Thomas Stuttaford***

The media covers PD inadequately, though better than it did 50 years ago. The reason is not that journalists are not interested in the condition, but that editors are interested in disasters that have a happy ending, and a chronic, degenerative disease such as PD does not fit that description. What about research-based stories? They are more inclined to cover these, but the discovery or advance has to be major. They are wise to charities trying to push anniversaries and awareness days, and are very unlikely to cover such events. However the PD community and the media should work together, because the media provides an estimated 85% of the general public's medical information. Other sources include the government and GPs, but they tend not to trust the former, and they are often overawed by the latter.

### ***Mary Baker***

Neurologists have not yet seen patients who have lived with PD for 40 years, but as the population ages, they will. A little girl born today in Tokyo has a 50% chance of living to 100. PD is expensive, and becomes more so the longer a patient lives with it. In 2007 the WHO estimated that of the total cost of the disease, nearly half is accounted for by loss of productivity.

PD is more than a movement disorder, and new models of care are needed, particularly multidisciplinary clinics. It's not that there is a shortage of neurologists per se, but that the neurologists need to work differently.

What do patients want? They want the neurodegeneration associated with PD to be slowed down or prevented, and the adverse effects of their medication to be reduced. They also want to be involved in clinical trials. The endpoints of those trials should be agreed with the patients, who know best what they should be. Access to new treatments should be accelerated for patients. To that end, the EBC and the European Federation of Neurological Associations has established a joint project, called Patient Access Acceleration. This will focus on two chronic diseases, one of which is PD (the other is multiple sclerosis).

Patient groups need to do more to achieve their own ends. They need to campaign on issues including reimbursement and counterfeit medicines. They need to understand health technology assessments, lobby policymakers and harness the media to communicate their goals to the wider public. Patients need to establish their credibility and collect evidence if they are to influence the debate.

### ***Discussion***

A medical student from the Netherlands asked how, if teamwork among medical specialists was the way forward, this was to be encouraged. Wolfgang Örtel emphasised the importance of introducing the collaborative concept during primary medical training, something that does not yet happen. For example, most doctors underappreciate other specialists with whom they should be working in the

management of brain disorders, such as physiotherapists and specialist PD nurses. Wolfgang Örtel also said that the neurology component of general practice training did not reflect the relative burden of brain diseases on the population. Every fourth patient entering the emergency room or casualty department is a brain disorder patient. Thomas Stuttford pointed out that neurology tends to be neglected in medical training for historical reasons, because pre-magnetic resonance imaging neurologists were considered a breed apart, so much did they have to know about the nervous system. Mary Baker and Suzanne Lindvall described a “buddying” project the EPDA has established, to teach European countries about successful multidisciplinary projects in other countries. A physiotherapist in the audience made the point that the concept of multidisciplinary teams was an element of physiotherapy training from day one. Manfred Westphal said that centres specialising in particular diseases already existed in Europe, within university medical faculties, and that students were free to seek them out. He also said that there was a lot of money available in Europe for projects in health delivery, though students were not taking it up because health delivery was not a “sexy” subject, or one that was going to get them many publications in high impact journals. Several people said that efforts needed to be made to change this perception. Steve Ford of the UK Parkinson’s Disease Society (PDS) said that the criteria the PDS lays down for its awards include teamwork.

Jes Olesen said there was a need to discuss best practice in Europe. Mary Baker said this would vary according to the country and the culture, but that there were universal principles, such as listening to the patient and thinking of PD as more than just a movement disorder. She would like multidisciplinary clinics such as the one in Nijmegen to collect health economy data, so that they can persuade others that their approach is cost effective. Tom Isaacs said that, from a patient’s point of view, multidisciplinary centres were absolutely crucial. A Dutch neurosurgeon, Michiel Staal, said that nobody questioned the benefits of such clinics for patients, but that it was a new concept in the medical field and there were practical problems in making them work, for example the need to overcome traditional communication barriers between disciplines, and have one specialist take the initiative.

Michael Rogers emphasised the importance of listening to citizens and taking the information they provide to policymakers. He repeated the point made by Commissioner Potočnik in his opening address, that the EC gives very little money itself, but that it can stimulate others to do so, and that the brain research community needs to push its case alongside those working in, for example, cancer. Mary Baker said that the brain community in no way wishes to take money away from the effort to combat cancer or heart disease, but that as medicine advances and cancer and heart patients survive those diseases and live longer, they are developing brain diseases. Therefore the burden of brain diseases is growing fast. Ian Ragan of the EBC added that funding brain research was an issue for the EU member states, which now had to move it up their agendas. He also said that the pharmaceutical

industry remained to be convinced that there was research worth funding in this area. Jes Olesen said the EBC was contributing to this goal by promoting collaboration and supporting the formation of National Brain Councils.

The issues of restless legs syndrome was raised. This, the most common of sleep disorders, receives no money from the EC but is about to get its own campaign group, under the leadership of Joke Jaarsma of the Netherlands. Thomas Stuttaford pointed out that neuropsychiatric diseases also tend to be neglected. He said that politicians whose jobs depend on votes could be swayed by the media, which speaks to and for the voters, and the medical community should therefore work with the media to influence policymakers.

Finally, Tom Isaacs asked if there was any way that clinical trials could be sped up, without compromising on safety, by allowing more patients to take part in them. Wolfgang Örtel called such trials investigator-instigated trials. He said there were difficulties that had to be overcome to run them, for example the need to invest in screening tools to find patients fast. However they do exist in Europe and their number is growing.

## **1<sup>st</sup> EBC Research Lecture**

### ***John Bowis***

This is a time of hope for those affected by PD, with new treatments and models of care becoming available. However, there is still no cure for the disease, and the number of patients is rising as the population ages. The number of people over 50 with PD is expected to double in the next 25 years. Tom Isaacs is one of the 8% of patients who develop the disease before the age of 40. The financial costs are rising too, leaving many people without access to care, and then there are the enormous emotional costs of PD to both patients and carers. The priority for society should be the most vulnerable, and there is a need for advocacy on their behalf.

As a society we must clearly state that we want science to reach as far as it can for the benefit of mankind, while at the same time listening to public concerns, for example about research involving stem cells or animals. I believe that primates should be replaced by other animals if possible, in research, and I back the new, tougher EC policy on animal research. The intention of the policy is not to restrict what scientists can do in terms of reducing the human disease burden, but merely to keep the pressure on them to limit the use of animals where possible.

Advocacy must also address the major problem of the stigmatisation of brain disease. There is a perverse reversal here, because those with brain disorders can run but they cannot hide. Such prejudice constitutes a human rights abuse, even if it is unintentional and born of ignorance. Services for those with brain disorders need to be as visible as the patients themselves. Medics, patients and politicians must

work with the media to address this issue, so that patients can, literally and figuratively, walk with their heads held high.

### ***Discussion***

Martyn Lewis asked if there would be an increasing emphasis on brain disease in Europe, and John Bowis replied that he was optimistic that there would be. He said that healthcare was regarded as key to the EU's Lisbon Strategy (2000), whose goal is to strengthen European R&D by 2010, because you can't have a healthy economy without healthy people. However, he warned that many disease specialties were competing for attention in Brussels, and advocacy for brain diseases was essential.

Jes Olesen said that stigmatisation was an important obstacle to recognition for brain diseases, because those affected tend not to talk about their condition. Martyn Lewis suggested that those indirectly affected by the disease—the 100 people that Suzanne Lindvall mentioned—could be mobilised to talk in their place. Jes Olesen emphasised the need to get the patients themselves talking, since this was a far more powerful weapon in the fight to increase awareness. John Bowis spoke about the need to emphasise the “can-do” aspect of brain diseases—the contribution that patients make to society and their continuing productivity, especially if their disease is well-managed.

### **Thursday 28 February**

#### **Opening address**

##### ***Manuel Hallen***

Under FP6 (2007-2010), the EC funded the area “Studying the brain and combating diseases of the nervous system” to the tune of €157 million, providing an extra €98 million for brain-related projects coming under other areas such as imaging and systems biology. FP7 (2007-2013) will show further commitment to the brain, for example in the introduction of public-private partnerships in research at the European level. An example is the Innovative Medicines Initiative, which will raise €2 billion for research (the EC and the pharmaceutical industry contributing €1 billion each). Another new feature of FP7 is a research area devoted to optimising the delivery of healthcare, whose aim is to speed up the transition of scientific advances from bench to bedside. As a result of the first two calls under FP7, 12 proposals will be funded to a total of €43.5 million, with an extra seven brain-related projects receiving €41.5 million in other areas. The project selection procedure is ongoing.

##### ***Tarun Dua***

The WHO coordinates global campaigns for neurological diseases with an emphasis on public health aspects, but it needs the support of stakeholders such as the EBC. Among its recommendations for action, the most important is that neurological care should be integrated with primary healthcare. Research priorities must also be

defined. In other words, its goals fit with those of the EBC. The WHO judges its efforts by their impact on the health of two vulnerable populations, Africans and women.

### ***Discussion***

Mary Baker said that a “quick and dirty” study in the northeast of England had found that primary care referrals to neurologists were very poor, and she wanted to know how, in the light of that, neurologists felt about being integrated with primary care. Jes Olesen said that national associations of neurologists had a responsibility to go out and teach general practitioners about referring patients. The system was not perfect, he said, but it fitted in with the “cascade” notion of teaching that the EBC is trying to encourage via its member organisations and national societies. Manuel Hallen wondered if it was for the neurologists to teach the primary physicians, or vice versa. Mary Baker said that the current referrals system discriminates against older patients. Patients under 40 are quite likely to be referred to neurologists, but that likelihood reduces with age, and after 80 patients have very little chance of seeing a specialist.

### **Keynote address**

#### ***Olle Lindvall***

Whereas brain repair was once considered impossible, we now know that partial reconstruction of neural circuits is possible. The principle behind stem cell research, in the context of neurological disease, is to restore lost brain function by replacing dead cells with new, healthy cells. PD is a possible application, since it is associated with a selective loss of dopaminergic neurons in the brain, but to date there have been no clinical trials of stem cell therapy in PD patients.

The evidence suggesting that stem cells might have a therapeutic application comes from experiments with foetal brain tissue (which is not the same as stem cells) implanted into PD patients’ brains. It has been reported that grafted neurons survive, integrate into existing circuits and produce a clinical improvement. Dopamine levels are restored to normal and are still normal after a decade. These experiments are considered proof of principle. However, the supply of foetal tissue is limited, and there have been other problems with this approach to date too, such as variability in the outcome due to poor standardisation of protocols.

Stem cells (embryonic stem cells, or neural stem cells from the adult brain) could in theory provide a plentiful supply of dopaminergic neurons, though it has not yet been demonstrated that dopaminergic neurons can be created from human stem cells. In the last 18 months, however, three major discoveries have brought us closer to this goal. Briefly, molecules have been discovered in animals that determine whether or not an embryonic stem cell will become a dopaminergic neuron; ways of culturing stem cell-derived neurons have been identified that enhance their survival; and,

perhaps most importantly, stem cells have been derived from genetically engineered human skin cells. These in turn have generated dopaminergic neurons that, when implanted into a PD animal model, ameliorate the deficit.

There are many problems still to be resolved before stem cell therapy reaches the clinic, for example the high costs, the efficiency with which cells can be generated and the lack of knowledge about how grafts will be affected by the disease. Even if we had an almost limitless supply of dopaminergic neurons, this form of therapy still would not be able to compete with DBS in terms of clinical outcome, so that outcome needs to be improved. A competitive treatment would have to be combined with a neuroprotective strategy to prevent disease progression.

There is currently much interest in molecules that may have neuroprotective properties, such as glial cell-derived neurotrophic factor (GDNF) and neurturin. These have been shown to counteract the death of dopaminergic neurons and to stimulate dopamine release, among other things. Gene therapy could be promising in this context, either in the form of direct delivery of the gene encoding the molecule of interest into the brain, or by delivering encapsulated cells that secrete the molecule (encapsulated cell biodelivery, or ECB). Trials of these approaches are either planned or underway.

In summary, to develop a clinically competitive stem cell therapy for PD, we need a new and efficient source of dopaminergic neurons, better patient selection and tailor-made transplantation procedures. Cell replacement and repair strategies should also ideally be combined with neuroprotection.

### **Panel discussion—theme three**

#### ***David Brooks***

When PD patients are enrolled in clinical trials, a frequent finding is that 10-15% of them have no dopamine deficiency. Also, a number of patients are diagnosed as having psychogenic or psychiatric PD, rather than “the real thing”. It turns out later that they do have “the real thing”; there is simply a strong psychiatric component to their disease.

Molecular imaging can help improve the accuracy of diagnosis of PD. The loss of dopaminergic neurons is not the only aspect of the disease that can be imaged; disease-related inflammation also shows up in scans. Drugs exist which can damp this inflammation and, in theory, slow the disease progression. PD dementia is associated with the accumulation of amyloid protein in the brain, which can also be imaged, and there are now methods for clearing amyloid.

Imaging can also be useful for detecting subclinical disease—for example, in people who have lost their sense of smell or who are related to a PD patient and therefore have an increased risk of developing the disease themselves—and for tracking the progression of their disease. Researchers are now working on neuroprotective

strategies. If these could be applied to individuals with the subclinical disease, it should theoretically be possible to prevent them from developing the full-blown, clinical disease.

Imaging can be used to monitor experimental neuroprotective therapies over time. It has already been used to look at the effects in the brain of GDNF infusion over six months, for example. The findings indicate that GDNF promotes the storage of dopamine. Though this says nothing about whether the dopamine was released and used as it should be, imaging could be used to address these issues too, and to correlate them with improvements in brain function. Finally, imaging can and is used by the pharmaceutical industry to look at whether molecules bind to their intended targets in the brain, and to gauge the dose of a molecule that affords the greatest therapeutic benefit.

### ***Pierre Pollak***

The mechanisms by which DBS reduces the symptoms of PD are highly complex, involving both inhibition and excitation of the brain. Most centres offering DBS need to improve their targets. First, however, a better understanding is needed of the pathophysiology of each symptom, since it is not always clear which target is related to which symptom. The pedunculopontine nucleus (PPN), a target that has been identified relatively recently, is a case in point. It is premature to claim that stimulating the PPN produces an improvement in postural instability and gait.

The safety of DBS also has to be improved. There is currently a high risk of adverse effects associated with the procedure, such as intracranial bleeding or contusion when the electrodes are implanted. Unresolved issues include whether there is a need for anaesthesia, and whether DBS should be applied to special patient groups, including those with hypertension or behavioural problems. Potential ways the procedure could be improved include stereotactic radiosurgery and transcranial magnetic stimulation (TMS), both of which are non-invasive. To investigate whether such improvements are feasible, controlled, randomised trials and better patient management are needed.

### ***Manfred Westphal*** (for *Andreas Engel, Hamburg University Hospital*)

To improve the efficacy of DBS, and to find out exactly where the electrode tips should be placed in the brain to produce the maximum benefit, we need to understand the neural networks that those electrodes are stimulating. To investigate these, in Hamburg we record from the electrodes as they are positioned during surgery. The neuronal firing patterns give us information about the networks the neurons in question belong to, and with careful analysis these can be distinguished like fingerprints. The results of such analyses can be used to guide the positioning of the electrodes. Since the patients are awake throughout their surgery, they can be asked to perform tasks, and the activity patterns associated with those tasks—both normal and pathological—can be observed.

This kind of technology is not suitable for all patients, and very careful patient selection is required. Ideally, they should be monosymptomatic. We mostly operate on rigid patients, because thanks to our electrophysiological analyses we know which neurons are responsible for rigidity, or akinesia. However, there is a lot of variability between patients, and each patient therefore serves as his or her own model. Patients have to be able to endure 12 to 14 hours of surgery, including several hours of recording.

The work of the Hamburg group shows that progress can be made when different specialities work together. A European consortium with a focus on intraoperative microrecordings would make even more progress, with a wider range of symptoms, patients and diseases.

### ***Thomas Gasser***

Rather than a disease, PD should be thought of as an assembly of pathological processes. In the last 15 years, at least 13 different loci and genes have been identified that contribute to what we traditionally call PD, but altogether they are only responsible for about 10% of all PD cases. So why are the genetics of PD considered so important?

There are two reasons: (1) The genes have taught us about cell mechanisms underlying cell death in PD. For example, three mutations in the alpha-synuclein gene have been linked with the disease. Lewy bodies, abnormal protein aggregates that form inside neurons, are a characteristic feature of PD and contain a form of alpha-synuclein. Since the formation of Lewy bodies is a key event in the disease pathology, this is an example of gene discovery directing researchers to the heart of the problem; (2) The most common PD gene discovered so far is PARK8 or LRRK2. The form of the disease associated with this gene is the most similar to sporadic PD, and the gene probably accounts for 2-3% of all sporadic cases in Europe. It is an autosomal dominant form of PD, so the siblings of an affected individual have a 50% risk of developing the disease themselves. This affords researchers an opportunity to identify high risk individuals who don't yet have symptoms, and to image their brains in the way that David Brooks has previously described, to identify when in the pathogenesis neuroprotective strategies might prove most effective. Understanding the genetics of the disease is also important for developing strategies that prevent cell death. Many other loci remain to be discovered for PD.

### ***Monica Di Luca***

What should European citizens be asking of scientists and doctors? Research must be strongly translational, moving quickly from the lab to the clinic. Intensive research is needed to understand brain function at all levels, in order to tackle brain diseases, and this will require a multidisciplinary approach.

Researchers are starting to decipher the mechanisms of cell death in PD. We now know, for example, that mitochondrial function is impaired, that there is an accumulation of abnormal proteins, a shift in the balance of oxidative stress and a failure of the proteasome (a cellular structure which degrades damaged or unneeded proteins). Proteomic analysis is leading to the identification of low abundance proteins and of their interactions with other proteins, which in turn is throwing up clues about their function. Researchers have learned that dopamine is not the only neurotransmitter of interest in PD. Glutamate also turns out to be important, and it seems that the interplay of the two at the neuronal junction or synapse may be important in the pathogenesis of PD. Certain, newly identified receptors also appear to be essential for the correct functioning of the synapse.

The challenges for the future include: achieving a better understanding of the underlying mechanisms of PD, with a view to designing neuroprotective strategies; developing new, chronic animal models; characterising the molecular mechanisms that lead to levodopa-induced dyskinesia (involuntary movements) and developing alternative therapies that prevent the onset of such adverse effects. We also need to build clinical and genetic imaging databases, and to identify and validate biomarkers that will enable doctors to diagnose subclinical disease reliably, using imaging.

### ***Werner Cautreels***

Duodopa is a gel composed of levodopa and carbidopa. Carbidopa inhibits the enzyme that converts levodopa to dopamine, but only outside the brain, thereby maximising the amount of levodopa that reaches the brain. The gel is delivered directly into the small intestine via a surgically implanted tube which is connected to an external pump. So it is a new delivery system for an old product, and it is used to treat advanced or complicated PD.

The traditional problem with levodopa has been that fluctuating levels of it in a patient's bloodstream can lead to switching between "on" and "off" states (dyskinesia-akinesia oscillation). Duodopa overcomes this problem by delivering a predictable and constant infusion of levodopa, resulting in continuous dopaminergic stimulation of the brain. Doses can be individualised to patients using a portable pump system. Each patient goes through a testing phase which involves applying the drug via a nasal tube, so that if it doesn't work they never proceed to the surgical implantation of the tube in their intestine.

Duodopa is not the final or best solution to treating PD, but we are working on further improvements to the system, and we are also developing strategies for patients at earlier stages of the disease.

### ***Discussion***

Tom Isaacs was concerned that scientists and doctors weren't talking to each other enough. David Brooks responded that there was close collaboration between basic

scientists in many different fields, and between basic scientists and clinicians. He said that funding bodies often direct research groups to collaborate with each other and highlight neglected but clinically important areas of research, such as the psychiatric aspects of PD.

Julien Mendlewicz of the European College of Neuropsychopharmacology said that in his field a lot of quality research was moving to the USA. He felt that Europe should confront the challenge posed by the fragmentation of research funding. Pierre Pollak said that although DBS was born in France, as a field it was now “truly international”. That meant that its funding was international too. He gave the example of a new study on the PPN (a brain target stimulated in DBS) that is being funded by both the Michael J. Fox Foundation in America and European sources.

Thomas Gasser made a plea for European level research in genetics. He pointed out that the first PD gene (for alpha-synuclein) was discovered in the US, the second in Japan, but that all the others had been discovered in Europe.

Mary Baker was worried that there were no eastern Europeans on the panel. Monica Di Luca said that eastern Europe had a strong research tradition and very good collaborations with the west. She pointed out that the European lecture at the US Society for Neuroscience’s annual conference in 2007 was given by a Hungarian. Zvezdan Pirtošek, a Slovenian neurologist, said that eastern Europeans need more of a voice in Europe, and perhaps the EBC could provide it for them. Olle Lindvall agreed that there was great talent in the east, which was being cultivated in the west. The trouble, he said, was that very often young eastern European researchers were learning to use technological platforms which were not available in their own countries, so that once trained they were obliged to remain in the west. The result was a brain drain in a westerly direction. Manuel Hallen said that the EC already provides structural funds to less developed EU regions, and that it was now prepared to fund research infrastructures there too.

Manuel Hallen also said that the EC was trying to prevent the fragmentation of funding but that, once again, it needed the support of EU member states to achieve its goal. He added that in a recent bilateral meeting between the EC and the US, the Americans had expressed concern that research funding in the US had plateaued. As a result they were not sure they could sustain their current levels of investment, and they asked that Europe fund more US scientists, in exchange for the funding that the US provides for European scientists.

## **Keynote address**

### ***Sir Michael Rawlins***

For any medical condition, it is necessary to have an infrastructure for appropriate healthcare delivery. That infrastructure depends on the local history, culture, political environment and approach to distributive justice (the principle on which limited

resources are shared out). There is huge variability in healthcare expenditure across the world. Turkey, for example, spends US \$500 per head annually, compared to \$6000 in the US. Yet, despite the vast US expenditure on health, it is only 29<sup>th</sup> in the world in terms of life expectancy, so healthcare is not just about money.

Given that a healthcare system relies on finite resources, it must be structured according to both clinical and economic evaluations. As far as clinical evaluation is concerned, I do not believe there is a hierarchy of evidence, with double blind, randomised trials at the top. All sorts of evidence can be useful. In economic terms, the UK's National Institute for Health and Clinical Excellence (NICE) tries to achieve a balance between efficiency and fairness. It does not take into account patients' loss of earnings, only the costs of the National Health Service and social services. This is partly because there are few data on patients' loss of income. However, an evaluation that did take productivity into account would automatically discriminate against the elderly (the group most affected by PD). The economic approaches NICE uses include cost minimisation, cost effectiveness analysis and cost utility analysis (using QALY). The probability that NICE will reject a strategy goes up with cost per QALY.

NICE's PD guideline covers diagnosis, interventions, communicating with patients, access to different kinds of care, palliative care and research recommendations. Economic evaluations were carried out for dopamine agonists as a first line treatment, and for DBS. The latter is considered highly cost effective under some circumstances. The recommendations for research include clinical evaluations of promising neuroprotective agents, and clinical and cost effectiveness evaluations of cholinesterase inhibitors, and of SSRIs for mild to moderate depression, as well as of supporting therapies.

All the evidence shows that clinical guidelines have the potential to substantially improve patient outcomes, however the methodology needs developing. The limitations include the still-crude tools for economic evaluation, the time-consuming nature of the process and the limited attention given to co-morbidities.

### ***Caroline Miltenburger***

In 2007, the UK's Alzheimer's Society published a shocking figure: £539 is spent on Alzheimer's disease per second in the UK. This kind of information is important for creating awareness of brain disorders, but also as a measure of the value of medical progress, for comparing different countries' approaches to healthcare, and for making decisions about resource allocation and reimbursement.

The EBC's CDBE study (2005) highlighted the very different costs per case of PD in different European countries. It was a remarkable study, because building a comprehensive database of such indicators tends to be a long and complicated process. Such studies are usually led by the launch of a new drug, rather than the desire to document a broad spectrum of diseases and costs.

There are, however, still many unknowns with respect to PD, in particular the lifetime costs of patients. How do costs change over the course of the illness, for example? We know that drugs are more important early on, and nursing home care later. Recent European studies have provided examples of methodologies that work for assessing such things. We would now like to launch a series of observational studies to estimate the costs of 12 brain disorders in Europe. The goal is to establish a robust evidence base to support patient advocacy initiatives and health economic models.

### **Panel discussion**

With respect to the desired emphasis on translational science, Olle Lindvall said that scientists are now forming translational consortia which include industry, so that whatever they develop is also competitive. However, he admitted that some basic scientists had never met a patient suffering from the disease they worked on. Mary Baker said that the pharmaceutical industry was increasingly asking patients to speak to their workforce, but overall she did not think that the PD community truly understood the meaning of the term “patient-centred”. Sir Michael Rawlins said that patient-centred meant two things: that the benefits of a strategy are what the patient wants (so not a biochemical test or an imaging technique), and that patients play an important part in the development of guidelines. NICE recognises that it can be a challenge for patients to converse with eminent neurologists, so it has set up a special unit whose remit is to help patients feel comfortable in the presence of specialists, and able to speak their minds. He said that patients brought a much-appreciated element of common sense to the table. Mary Baker asked if that attitude pervaded all levels of the medical community, including general practitioners, and Sir Michael Rawlins said that it did so increasingly, though with some geographic variation.

Irish PD patient Ann Keilthy raised the controversial issue of how NICE evaluates the cost effectiveness of treatments. She received DBS seven years after her diagnosis and regained 75% of her former productivity, being able to return to work following her treatment. She wanted to know why people weren't getting access to DBS early in the disease, when it could make a dramatic difference in their productivity. Sir Michael Rawlins repeated his point that NICE did not take productivity into account, and warned that if it did older patients would suffer. Jes Olesen questioned the assertion that the resources available for healthcare were finite. He regretted the shift towards perceiving health only in terms of cost effectiveness, rather than in human terms too, and he suggested that, with effective campaigning, the resources dedicated to health could be expanded, both in nation states and in Europe as a whole. Martyn Lewis pointed out that health was not a government's sole priority. Manfred Westphal said that Europe was not good enough at patenting the fruits of its research, and that this would affect healthcare costs in future.

Mary Baker emphasised the importance of research in the social sciences, particularly when it came to establishing models of good service delivery. Manuel Hallen said that the EC already funds such research through a special programme. In addition, non-governmental organisations that receive EC funding are required to report back to it, and that feedback is a valuable source of information. Mathilde Leonardi, an Italian neurologist, asked how strong the links were between the various directorates-general (DGs) of the EC, since social science research often fell between the remit of two of these (most often DG Research and DG SANCO (Health and Consumer Affairs)). Hallen replied that the DGs communicated with one another well, and were used to developing common strategies.

The discussion turned to the EBC's consensus document on European brain research (2006), and ways that it could be updated or improved. Joke Jaarsma of the Netherlands said that, as the most common sleep disorder, restless legs syndrome should have been included in the list of brain disorders studied. Julien Mendlewicz point out that it was mentioned in theme five, under sleep disorders. Jes Olesen emphasised that the existing document must be seen as a starting point, because at the time it was drawn up many data simply didn't exist. Manuel Hallen welcomed the initiative, but said that the document seemed to demand more money from the EC, when it is the member states who must really invest more. Michael Rogers said that more emphasis should be placed on the strength Europe can gain through its diversity, and that member states should be encouraged to learn from each other. Sir Michael Rawlins said he would have liked to have seen the research organised by cross-cutting themes, for example the accumulation of abnormal proteins which is a feature of so many neurodegenerative disorders. The EC could encourage this cross-disciplinary approach, he said. Manuel Hallen responded that member states would have to give the EC the mandate to look at healthcare in a Europe-wide fashion, which they had not yet done. Sir Michael Rawlins also felt that the document should refer to clinical trial networks.

Summarising the recommendations for improving the consensus document, Jes Olesen said that information about clinical trial networks could be added to each two-page theme, and that information about social sciences research could also be included. Anyone with any further suggestions was asked to email them to Evelyn Sipido, EBC Liaison Officer, at: [evelyn.sipido@unifi.it](mailto:evelyn.sipido@unifi.it)

### **The way forward**

Mary Baker highlighted the importance of charters, which are drawn up by the people for the people. She said the WHO's Neurology Atlas had paved the way for The Global Declaration on Parkinson's Disease (1997), which had been incredibly helpful in raising awareness of the disease around the world, and that the EBC was putting its full support behind National Brain Councils in Europe, of which there were already five, with the same rationale.

Mary Baker and David Vodusek of Slovenia then launched The Brain Charter for Europe. The charter aims to have brain diseases recognised as a public health issue, raise awareness, promote cooperation within and between member states on the management of brain diseases, encourage funding for research, and strengthen partnership between all stakeholders. Mary Baker said that Commissioner Potočnik had promised to sign the charter.

Paul Arteil of GAMIAN (Global Alliance of Mental Illness Advocacy Networks)-Europe, said that putting the patient at the centre of a dialogue about how best to tackle brain disease should be a principal challenge for the years to come. This meant developing a language patients could understand and going out to see them, rather than inviting them in. Finally, Mary Baker said that partnership, informed debate, a multidisciplinary approach and the need to address research by cross-cutting theme were all messages to be taken away from the meeting.