

## **Neuroscientist Marius Maxwell sets the record straight on Parkinson's research**

**In the following open letter to VERO, Oxford University alumnus Marius Maxwell MBBChir DPhil (MD PhD) strongly refutes the often repeated claim that the deep brain stimulation technique used to treat Parkinson's disease patients has its origins in primate research. On the contrary, he argues, the technique was first developed in humans decades before the first monkey model of Parkinson's was ever conceived. In a detailed chronology of the research undertaken in this field over the last century, Maxwell demonstrates that all the major advances in the treatment of movement disorders have come about through the study of actual human patients, not contrived animal models. To suggest otherwise is, according to Maxwell, to distort the true historical facts and ignore the key contributions of earlier, pioneering neuroscientists. Worst of all, the continued justification and funding of primate research for Parkinson's disease and similar disorders is hampering the development of other, more progressive and humanly relevant techniques, and hence delaying the discovery of a definitive treatment for the disease. In conclusion, Maxwell therefore calls for an immediate end to such research, in the interests not just of the defenceless animals on whom it is conducted, but of the human patients still awaiting a cure for their debilitating disease.**

**The full text of Marius Maxwell's letter is below.**

### Open Letter to VERO

from Marius Maxwell, MBBChir DPhil (MD PhD)

Dear VERO,

#### *Lies, Damned Lies and Monkey Science*

The abuse of primates in medical research for Parkinson's disease lies at the very epicenter of the debate about the scientific relevance of vivisection to human health today. Time and time again, I read the extraordinary misstatement that the MPTP-primate model demonstrated the pivotal role of the subthalamic nucleus and led to the development of deep brain stimulation in Parkinson's disease.

This claim is a clear misrepresentation of the historical record which actually shows that neurosurgical experimentation with cohorts of human patients, performed decades before the very first description of the MPTP-primate model, has alone led to the present treatment of deep brain stimulation in Parkinson's disease.

Because human research itself culminated in the technique of deep brain stimulation in Parkinson's disease, one can only conclude that primate vivisection has amounted to an expensive, savagely cruel, and scientifically invalid sideshow. It inhabits a parallel universe of biomedical curiosity if you will, drawing from but contributing nothing to *bona fide* human scientific discoveries in Parkinson's disease. All it has done is to reinvent the wheel of Parkinson's disease research over and over again. And yet despite this, astonishingly, the MPTP-primate model of Parkinson's disease is still held up by some as the poster child for justifiable vivisection. Let us therefore examine this proposition closely.

The basal ganglia are a group of deep brain nuclei which are essential to the control of body movements and posture, among other functions. Their disruption upsets a delicate interaction, modulated by neurotransmitters such as dopamine, which results in movement disorders such as Parkinson's disease. Used as an adjunct to anti-Parkinson drugs when their efficacy starts to wane, deep brain stimulation uses indwelling electrodes, placed stereotactically into the basal ganglia nuclei and powered by an implanted battery unit, to alleviate the motor symptoms of the disease.

Of the several nuclei comprising the basal ganglia, stimulation of the subthalamic nucleus by deep brain stimulation in Parkinson's disease patients is the surgical treatment of choice in most centers internationally. Deep brain stimulation of the subthalamic nucleus is more effective than medical management alone, but the frequency of serious adverse side effects, including fatal intracerebral haemorrhage, is more than three times higher with deep brain stimulation than with medical management alone (Deuschl *et al.* 2006; Weaver *et al.* 2009). In all cases, Parkinson's disease patients need ongoing medical care during the inexorable progression of their crippling disease.

The treatment of Parkinson's disease by deep brain stimulation is now used worldwide and has been employed in some 40,000 patients with movement disorders. Deep brain stimulation is not a cure for Parkinson's disease, which is a chronic and progressive neurological disease. Although this procedure can improve the movements of patients with Parkinson's disease, it does not affect the host of other disabling non-motor symptoms such as cognitive decline, memory loss, imbalance, anxiety and depression. In some cases, it can exacerbate these non-motor issues and in others can cause new problems including an increased incidence of suicidal depression.

However, no-one disputes the importance of deep brain stimulation in Parkinson's disease, and therefore it is most pertinent to ask how this technique was really discovered.

The "official" and highly selective primate vivisection-based narrative of deep brain stimulation misleadingly begins with the serendipitous discovery of symptoms of parkinsonism in young drug addicts exposed to the narcotic contaminant MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). This gave researchers the idea of seeing whether monkeys would also display Parkinsonian symptoms in response to this toxin and indeed, in 1983 monkeys poisoned with MPTP were found to exhibit similar, albeit temporary, symptoms and the non-human primate model of parkinsonism was born (Burns *et al.* 1983).

From 1989 to 1990 - so the story goes - recordings in MPTP-treated monkeys then revealed over-activity within the subthalamic nucleus, which in turn led to the demonstration that lesioning it completely reversed the experimental chemical parkinsonism (Mitchell *et al.* 1989; Alexander *et al.* 1990; Bergman *et al.* 1990).

This account continues with the discovery that the implantation of stimulating electrodes in the subthalamic nucleus of humans with Parkinson's reversed many of the disease's most crippling symptoms (Benabid 1987; Limousin 1995). In this way, we are repeatedly told, deep brain stimulation was created by the endeavours of monkey researchers.

All well and good, it seems. The general public is served a compelling tale of successful medical research borne on the back of primate misery and has come to believe that human sufferers of the ravages of Parkinson's disease have been treated thanks to cutting-edge research performed on our close primate cousins.

But what will they say when they find out that the importance of the subthalamic nucleus to the treatment of Parkinson's disease had in fact been known more than 30 years before by neurosurgeons who employed this knowledge to successfully treat hundreds of human patients? How will they react when they discover that deep brain stimulation has been used since the 1940s, and that early implanted stimulators were used in human patients with Parkinson's and other movement disorders years before the first ever description of the MPTP-primate model?

Hundreds of monkeys have been experimented on, countless "peer-reviewed" articles have been written, and a vast archive of monkey "data" has been accumulated for sure but, as we shall see, deep brain stimulation in Parkinson's disease developed without this.

Indeed, since the incremental clinical human research which led to the current use of deep brain stimulation in Parkinson's predated by many years the very first description of the MPTP-primate model in 1983 (Burns *et al.* 1983), how on earth could the latter account for the former? If this were true, it would place the cart four square before the horse!

The rich and storied history of functional neurosurgery, including that of movement disorders such as Parkinson's disease, spans well over a century since the neurosurgical pioneer Victor Horsely reported the first surgery to treat dyskinesia in 1890 (Horsely 1890).

In the 1930s, surgery of the basal ganglia was considered to be *noli me tangere* ("let no one touch me") when Walter Dandy, one of the fathers of neurosurgery, issued this admonition after observing the crippling effects of strokes in this region and concluded that the 'seat of consciousness' must reside there (Dandy 1966). This caution of the dangers of basal ganglia surgery was echoed by Bucy who also held that patients relieved of Parkinsonian symptoms would necessarily suffer paralysis and other devastating complications (Bucy 1939).

Luckily, these fears were subsequently laid to rest by Meyers in 1939, who excised the head of the caudate nucleus of a patient with Parkinson's disease with resulting alleviation of symptoms unattended by the feared complications of paralysis or unconsciousness (Putnam 1966). He went on to describe 58 further basal ganglia procedures for the treatment of patients with Parkinson's disease before 1949 (Meyers 1968).

These great strides in movement disorder research were made solely in human patients, and the few

scattered and contradictory animal studies of the 1930s and 40s were no more predictive or even scientific than such studies are now. The refinement of existing stereotactic techniques in 1947 ushered in a new and far more precise era for the surgical treatment of Parkinson's disease and other movement disorders (Spiegel *et al.* 1947; Spiegel and Wycis 1950). This enabled neurosurgeons to operate on the brain using three-dimensional pinpoint accuracy aided by precise coordinates obtained from human post-mortem brain atlases.

Deep brain stimulation has been routinely performed since this improvement in stereotaxis in 1947 (Spiegel *et al.* 1947), and in the ensuing several years multiple basal ganglia targets in human patients were empirically tested using both low and high-frequency deep brain stimulation for the treatment of symptoms of various motor disorders including Parkinson's disease.

This deep brain stimulation was used to identify the target basal ganglia nucleus, avoid vital surrounding structures like the internal capsule (damage to which would cause paralysis), and conduct neurophysiological studies (Spiegel and Wycis 1952; Spiegel *et al.* 1963). In parallel with this stereotactic neurosurgical treatment of movement disorders, therapeutic development of deep brain stimulation continued apace from 1947 onwards through implantation of electrodes during psychosurgery with relief of both pain and abnormal movements as benefits (Heath, 1954; Pool *et al.* 1956; Mazars *et al.* 1980).

*This discovery and use of deep brain stimulation therefore predates the very first description of the MPTP-primate model of Parkinson's disease by nearly 40 years! As we shall see, deep brain stimulation would not realise its full potential until 1980 when a fully implantable and reversible stimulator system for movement disorders was developed, this still a full three years before the Parkinson's disease MPTP-primate model was even first described.*

*Successful surgery of the subthalamic nucleus was first reported in 1963 by OJ Andy, some 30 years before being performed in MPTP-lesioned monkeys. He studied over 50 patients with Parkinson's disease and evaluated the optimal lesion site using radiofrequency deep brain stimulation (Andy *et al.* 1963). Story *et al.* also performed successful lesions of the subthalamus in 50 patients with Parkinson's disease in 1965 and reported that tremor and rigidity were improved in 62 per cent of them (Story *et al.* 1965). In that same year, Mundinger also carried out subthalamotomies in a series of Parkinson's disease patients (Mundinger 1965), and in 1968 Fager also studied subthalamic nucleus lesions in a large cohort of 80 Parkinson's patients (Fager 1968).*

*These surgeries were performed on the subthalamic nuclei of over two hundred Parkinson's disease patients nearly a full three decades before the claimed "discovery" of the importance of this nucleus was reported in the MPTP-primate model (Bergman *et al.* 1990).*

The advent of a successful drug therapy for Parkinson's disease in 1968, in the form of L-Dopa, led to a precipitous decline in the need for stereotactic neurosurgery, including that of the subthalamic nucleus, for the treatment of Parkinson's disease. However, despite this pharmacological success, the following 20 years saw increasing numbers of patients who became unresponsive to the drug and who developed drug-induced movement abnormalities called dyskinesias. Stereotactic neurosurgical treatment for Parkinson's disease would have to wait until 1992 before being revived (Laitinen *et al.* 1992a, b). By then the MPTP-primate model was in full swing and the real origins of neurosurgical treatment of Parkinson's disease were completely ignored.

Further studies of therapeutic deep brain stimulation were described in patients with movement disorders including Parkinson's disease who were treated by the stereotactic implantation of electrodes with interval stimulation being performed two to three times per week (Bechtereva *et al.* 1972, 1975).

The logical advance in therapeutic deep brain stimulation then occurred in the late 1970s with the introduction of permanently implantable stimulators for deep brain stimulation based on the development of miniaturized battery-powered cardiac pacemakers. It was not long before the destructive lesions were replaced by implantable stimulators which were adjustable, reversible and non-destructive. Starting in 1975, Mundinger used deep brain stimulation of the ventrolateral thalamus for the treatment of movement disorders and reported successfully treated cases in 1982 (Mundinger and Neumuller 1982).

Brice and McClellan implanted deep brain stimulators to target the region of the subthalamus, thereby controlling the tremor of patients with multiple sclerosis in 1980 (Brice and McLellan 1980). Cooper *et al.* used deep brain stimulation of the ventrolateral thalamus and reported encouraging results in patients with cerebral palsy (Cooper *et al.* 1982). Siegfried went on to demonstrate the successful use of deep brain stimulation in the thalamus of patients for chronic pain and dyskinesia (Siegfried *et al.* 1986, 1987).

*Finally, at this point of advanced understanding of the surgical manipulation of the subthalamic nucleus and other basal ganglia together with the use of implantable therapeutic deep brain stimulation in patients with movement disorders including Parkinson's disease, the MPTP-primate model of parkinsonism was first described (Burns et al. 1983).*

Benabid, knowing of the importance of the subthalamic nucleus to Parkinson's disease from the surgical studies of 1963 and subsequently, together with the more recent data of deep brain stimulation in patients with Parkinson's disease and other movement disorders, took the logical and incremental next step by reporting the benefit of stimulation of the subthalamic nucleus in 1995 in a series of patients (Limousin *et al.* 1995).

The oft-parroted claim that "the MPTP monkey model demonstrated the pivotal role of the subthalamic nucleus in the mechanisms central to Parkinson's disease" is therefore clearly false. Furthermore, it does a grave disservice to the memory of the many real pioneers of neurosurgery by co-opting their repeated demonstration of the very same, decades before. It is as if they have been quietly airbrushed from the pages of history.

As Bertrand Russell rightly maintained, the fact that an opinion is widely held is no evidence whatsoever that it is not utterly absurd.

Most importantly, the rapid and reversible MPTP-induced parkinsonian state in monkeys bears little relation to the slowly progressive and irreversible Parkinson's disease, which is unique to humans. The pathological differences between the two are profound and the idea that the former can act as a predictive model for the latter flies in the face of the basic tenets of evolutionary biology. The only real "model" of Parkinson's disease has been found in the tissues of the very patients who

suffer from it, as the true historical narrative demonstrates only too well.

None other than the towering figure of the late Nobel Laureate Francis Crick was also a harsh critic of the experimental use of primates in the neurosciences. In a paper aptly entitled 'Backwardness of human neuroanatomy' (Crick and Jones, 1993) he complained:

*"What is known about the neuroanatomy of the human brain? Do we have a human cortical map corresponding to that for the macaque? And what does the human equivalent of the connectional map look like? The shameful answer is that we do not have such detailed maps because, for obvious reasons, most of the experimental methods used on the macaque brain cannot be used on humans. For other cortical regions, such as the language areas, we cannot use the macaque brain even as a rough guide as it probably lacks comparable regions."*

Crick argued for the development of new and forward-looking techniques with which to study the anatomy of the human brain.

*"To interpret the activity of living human brains, their neuroanatomy must be known in detail. New techniques to do this are urgently needed, since most of the methods now used on monkeys cannot be used on humans."*

He maintained that molecular techniques would have a revolutionary impact on systems neuroscience, a prediction that has been largely fulfilled.

Despite these fundamental criticisms from such unimpeachable authorities, a broad and profitable industry of primate modeling for human disease has grown. Like a great edifice built on foundations of sand however, its basic scientific structural integrity remains very much open to question.

The most profound ethical concerns surrounding non-human primate research are paid scant attention - no more than lip service, really - by those who benefit professionally from it. No-one has hitherto attempted to defend their experimentation upon ethical grounds, but their continuing justification of such vivisection on professed "scientific" grounds is easily exposed and refuted by any broad and unbiased examination of the historical record. The few remaining proponents of such vivisection are fully entitled to their own opinions but not to their own facts or to historical revisionism.

It is vital to remember the absolute obligations of researchers to integrity in the scientific method, to the fundamental needs of their patients, to the increasingly cash-strapped institutions which fund their endeavours, and last but not least to the inviolable rights of the hapless and wretched monkeys upon which they experiment.

Persistent support for the non-human primate MPTP model of Parkinson's can only serve further to neglect and impoverish the demonstrably scientific and productive avenues of the clinical neurosciences, including neurosurgical, radiological, pathological, epidemiological and molecular

biological research into human patients themselves.

The predictable consequences of maintaining the *status quo* will be further obfuscation and delay in the discovery of a definitive treatment for Parkinson's disease. The real interests of those sufferers of Parkinson's disease and other movement disorders can, therefore, only be served by the immediate cessation of this transparently unscientific and wholly indefensible exploitation of non-human primates.

Marius Maxwell

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