HISTORY OF MEDICINE

Parkinson's disease and primate research: past, present, and future

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Scientific research involving non-human primates has contributed towards many advances in medicine and surgery. This review discusses its role in the progress made towards our understanding of Parkinson's disease and its treatment. Established medical treatments like dopamine agonists continue to need primate models to assess their efficacy, safety, and mechanism of action. The recently developed treatment of deep brain stimulation of the subthalamic nucleus required validation in primates before entering the clinic. Controversies surrounding future treatments such as gene therapy show the need for properly evaluated preclinical research using appropriate animal models before progression to clinical trials. Research on primates has played—and continues to play—a crucial part in deepening our understanding of Parkinson's disease, improving current therapies, and developing new treatments that are both safe and effective. In animal research, the ''three Rs'' of humane technique—reduction, refinement, and replacement—should be adhered to.

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The Research Defence Society recently released its 2005 *Declaration on Animals in Medical Research*, signed by over 500 leading British physicians and scientists.[1] It states:

> ''Throughout the world people enjoy a better quality of life because of advances made possible through medical research, and the development of new medicines and other treatments. A small but vital part of that work involves the use of animals.''

The new declaration also reaffirms the 1990 statement:

> ''Experiments on animals have made an important contribution to advances in medicine and surgery, which have brought major improvements in the health of human beings and animals.''

Our current understanding of the pathophysiology and treatment of Parkinson's disease (PD) exemplifies these statements. Animal research, and in particular non-human primate research, has led to many recent medical and surgical treatments, and also opened the way for several exciting therapeutic prospects to help combat the increasing burden of this disease in our ageing population.

In his original 1817 ''essay on the shaking palsy'', Parkinson stated that ''until we are better informed respecting the nature of this disease the employment of internal medicines is scarcely warrantable''.[2] C D Marsden, a renowned authority on movement disorders, commented in 1975 that ''although it is possible to study many aspects of basal ganglia function in laboratory rodents, much of the research into experimental parkinsonism and dyskinesias must be undertaken in primates, for only those animals develop the typical clinical phenomena seen in man''.[3] A consideration of the past, present, and future contributions of primate research to PD is timely nearly two centuries since Parkinson's observations and three decades on from Marsden's astute insight.

PARKINSON'S DISEASE AND MOVEMENT DISORDERS

The term movement disorders has come to refer to those neurological diseases that cause disorders of movement not attributable to motor weakness or spasticity, sensory loss, or to cerebellar ataxia.[4] Movement disorders are characterised either by poverty and slowness of movement and increased tone (akinetic-rigid syndromes), or by abnormal involuntary movements (dyskinesias)—the main types of dyskinesia are tremor, chorea, myoclonus, tics, and dystonias. Table 1 lists many of the more common movement disorders. Most movement disorders occur with dysfunction of the subcortical brain structures comprising the basal ganglia (fig 1).

In Parkinson's original description of PD, he gave an account of six cases in which he noted signs of tremor, festinating gait, flexed posture, and ''lessened muscular power''.[2] A memorable acronym for the PD motor sequelae is TRAP, a mnemonic for tremor, rigidity, akinesia, and postural imbalance. PD is a slowly progressive, degenerative disease, and is the most common movement disorder in middle or late life with a prevalence of about 0.1% in the UK, rising to 0.5% in people over 50 years of age; about 130 000 people suffer from it in the UK.

Abbreviations: 6-OHDA, 6-hydroxydopamine; DBS, deep brain stimulation; GABA, γ-aminobutyric acid; GDNF, glial cell line derived neurotrophic factor; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease

Parkinsonism exhibits the same TRAP signs as PD, but with a known aetiology such as drugs or encephalitis, more sudden onset, and often occurring earlier in life.

The main pathological finding in PD is loss of the neuromelanin-pigmented neurons in the substantia nigra of the basal ganglia with associated gliosis, and its cardinal biochemical feature is dopamine deficiency in the striatum, another basal ganglia structure.

PAST

Initial discoveries

Parkinson originally attributed the disease to medullary swelling impeding the passage of nervous influence from brain to muscle.[2] A role for the basal ganglia in movement disorders was not popularised until half a century after Parkinson's original description of PD. In 1868 Hughlings Jackson's primate research and observations of patients led him to suggest that unstable basal ganglia activity led to chorea.[5] His postulates were supported by Sherrington's development of the decerebrate animal as a plausible model of parkinsonian rigidity.[6]

Nearly a century on from Parkinson's original description, soon after Wilson had described hepato-lenticular degeneration in the disease that came to bear his name,[7] Ramsey Hunt postulated a theory whereby lesions to different components of the basal ganglia could cause not only chorea, but also parkinsonism and athetosis.[8] His theory built on Wilson's findings from lesions made in primate basal ganglia and cerebral cortex using Horsley and Clarke's recently invented stereotactic apparatus.[9] Inhibition release hypotheses similar to those of Hughlings Jackson, Ramsey Hunt, and Wilson prevailed until two decades ago although they fail to explain many symptoms and signs of movement disorders, such as the great variety of motor manifestations of Huntington's disease. The basal ganglia remained unfathomable ''dark basements of the mind''.[10] Nevertheless, theories and laboratory models of the time provided sufficient impetus for multifarious attempts at surgical lesioning to ameliorate parkinsonian symptoms throughout the first half of the 20th century.

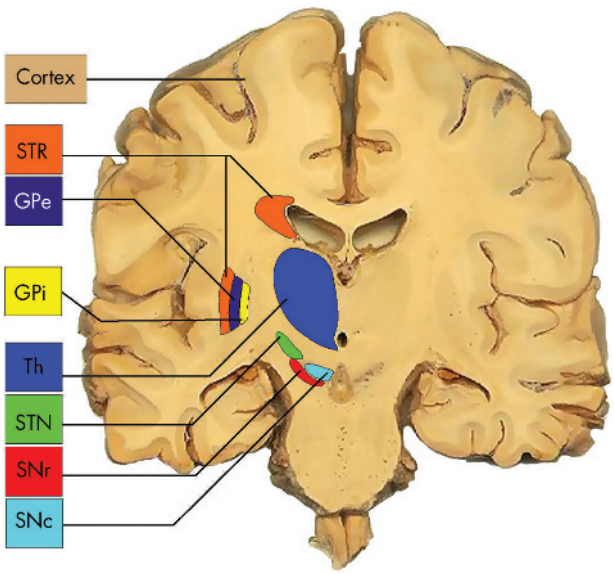

Figure 1 The basal ganglia shown in a coronal view of the brain. STR, striatum; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; Th, thalamus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata.

Table 1 Movement disorders

Akinetic-rigid syndromes	Dyskinesias
Parkinson's disease	Tremor (many causes)
Parkinsonism	Sydenham's chorea
Drug induced parkinsonism	Huntington's disease
Juvenile parkinsonism	Hemiballism
Post-traumatic parkinsonism	Myoclonus (generalised or focal)
Infectious (for example, encephalitis/prion disease)	Gilles de la Tourette's syndrome
	Torsion dystonia
Other (for example, hydrocephalus/paraneoplastic)	Primary dystonia
	Paroxysmal dyskinesias
Other	Focal adult-onset dystonias (for example, spasmodic torticollis)
Multiple system atrophy	
Wilson's disease and other hereditary metabolic disorders	Drug induced tardive dyskinesias
Progressive supranuclear palsy	
Cortico-basal degeneration	
Diffuse Lewy body disease	

The counterintuitive, albeit now vindicated, strategy of using surgical lesioning to improve an already impaired nervous system has its origins both in the clinic and in primate research. Parkinson himself noted that the resting tremor of one of his patients disappeared with a stroke that rendered them hemiplegic. In addition to Sherrington's observations in decerebrate animals including primates, a series of experiments by Fulton during the 1930s using primates and other animals showed that tremor arising from cerebellar damage was relieved by lesions to the motor cortex,[11] a finding interpreted by Bucy among others to be applicable to parkinsonian tremor.[12]

While many surgeons targeted the basal ganglia, targets varied dramatically in brain and spine, and even included thyroidectomy.[13 14] Most had little success. As Laitinen put it, ''When one sets out to make a historical survey of surgical attempts to relieve the tremor and rigor in Parkinson's disease, one cannot help feeling that it would have been a far easier task to list those nervous structures which have not been attacked''.[15]

Rapid recent progress

In 1952, the American neurosurgeon Cooper operated upon a patient with PD and inadvertently ligated their anterior choroidal artery causing infarction of a basal ganglia structure called the globus pallidus. Despite the damage done, his patient awoke with their tremor resolved and no deficits.[16] Cooper's finding led to the relatively effective practice of injecting alcohol into the globus pallidus. That same decade, Leksell capitalised upon Cooper's discovery, using thermocoagulation together with his recently invented stereotaxic apparatus to accurately lesion the globus pallidus to ameliorate parkinsonian hypokinesia and rigidity in over 200 patients.[17–19] Nevertheless, little had been revealed mechanistically regarding the dysfunctional circuitry underlying PD and other movement disorders.

However, theoretical advances were soon made in the 1960s when evidence from lesions to the basal ganglia of primates led to the development of important proposals by Denny-Brown relating movements to muscle tone. He suggested that movement is a change of posture, and thus that movement disorders arise from conflicts between postural reflexes because of basal ganglia dysfunction.[20 21] The 1960s also saw the advent of levodopa as a viable therapy for PD—in 1967 Cotzias reported dramatic improvements in PD patients receiving high dose levodopa treatment.[22] His seminal work and subsequent clinical trials that cemented levodopa's place as the mainstay of PD drug therapy were inspired by research showing reversal of akinesia with

levodopa in reserpinised animals, thus implicating dopamine deficiency in PD.[23]

It was not until the 1980s when data had been gathered from several years' worth of studies of single neuron activities in awake, moving primates that a theory for basal ganglia function could be postulated that could explain the symptoms and signs of PD and other movement disorders.[24] The experiments of DeLong, Crossman, and others led to a proposal that the circuitry comprising direct and indirect pathways was dysfunctional in many movement disorders (fig 2), and also that parallel circuits linking cerebral cortex structures with the basal ganglia were involved in cognitive and emotional processing. Dysfunction in such a parallel cortico-striato-pallido-thalamic neuronal network provided a plausible paradigm to explain many of the cognitive and emotional problems associated with movement disorders, like the concomitance of depression and PD.[25]

Within the past two decades, much research has been conducted towards elucidating the roles of the basal ganglia in PD, other movement disorders, and psychiatric illnesses.[26 27] Outlined below are some fundamental advances made in primate research that lead to current therapies and future prospects for the treatment of PD.

PRESENT

Current treatments

In 1983 several cases of parkinsonism seen in heroin users led to the discovery that the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces parkinsonism in humans.[28] This led to the development of a primate model of parkinsonism that remains the only mammalian model to exhibit the resting tremors and drug induced dyskinesias seen in humans.[29] Alongside the electrode studies mentioned above, metabolic marker experiments using this model

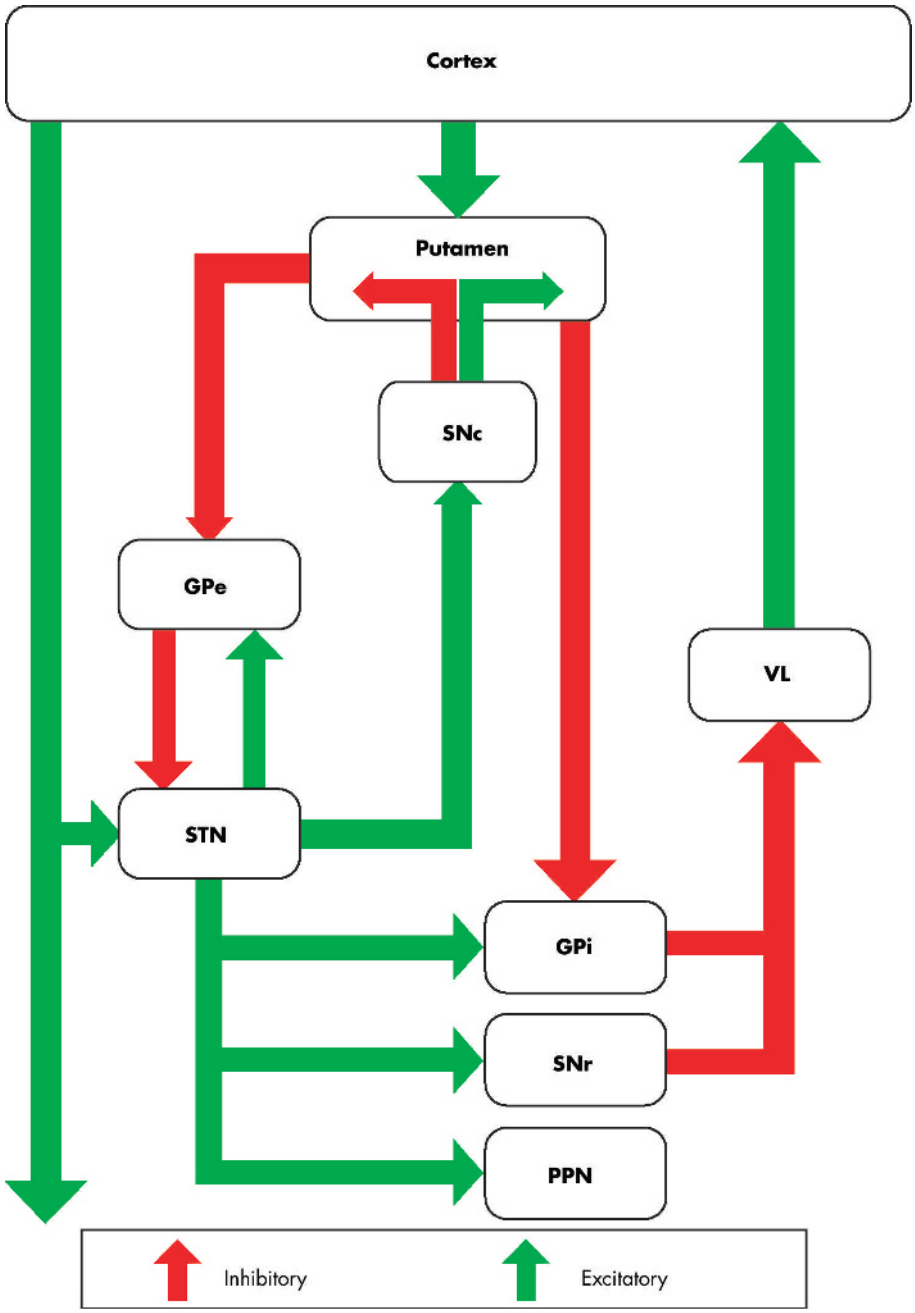

Figure 2 Direct and indirect pathways in the basal ganglia. GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VL, ventrolateral thalamus; PPN, pedunculopontine nucleus.

showed much about activity in basal ganglia circuits.[30] In the early 1990s, it was shown that lesions made to the subthalamic nucleus of the basal ganglia in primates reversed the motor symptoms of MPTP induced parkinsonism.[31 32] Together with the resurgence of globus pallidus lesioning surgery pioneered in Sweden in the late 1980s for movement disorders refractory to drug treatment,[33 34] this finding led to a veritable renaissance in neurosurgical treatment for PD.

Reversible lesions of the subthalamic nucleus by deep brain stimulation (DBS) using bilaterally inserted indwelling electrodes have dramatically improved signs and symptoms of PD enabling patients to reduce their levodopa dose radically (fig 3).[35–37] To date worldwide about 30 000 patients with PD have benefited from DBS. However, the procedure will probably remain limited to specialist centres, and appropriate patient selection is crucial to its successful use.[38] Few randomised clinical trials of DBS have been done,[39] although a large multicentre trial, PD SURG, is currently underway in the UK (http://www.pdsurg.bham.ac.uk).

Current anatomical models of basal ganglia function (fig 2) fail to explain wholly the efficacy of DBS in PD, in particular the finding that stimulation of the globus pallidus interna paradoxically improves dyskinesias without deleterious effects upon motor function,[40] although primate research continues to further our knowledge in this regard. One elegant postulate gaining popularity draws upon primate and clinical data implicating aberrantly modulated rhythmic activity in different basal ganglia neurons oscillating in synchrony at different frequency bands to account for both the pathological movements of PD and the efficacy of surgical lesions and DBS at different basal ganglia sites.[41] Further research is needed, both experimentally in animals including primates, and from patients to gain a fuller understanding of such mechanisms. Primate research also continues to show new roles in PD for other brain structures outside the basal ganglia like the pedunculopontine nucleus.[42] These findings provide exciting possibilities for DBS and other therapeutic modalities.

As an alternative to MPTP, the neurotoxin 6-hydroxydopamine (6-OHDA) has recently become popular in primate research. Neither the MPTP nor the 6-OHDA models of parkinsonism are perfect and their utility and limitations have been comprehensively reviewed.[43–47] Despite their successful emulation of parkinsonian symptoms, one particular shortcoming is their inability to replicate the insidious onset and progressive degeneration seen in PD. Nevertheless they are accurate enough to have proved invaluable to the preclinical investigation of pharmacological treatments. Many drugs for movement disorders have been investigated using primate models. Most notably our understanding of levodopa has been greatly improved by primate research directed at prolonging and improving its beneficial effects and reducing side effects like dyskinesias. Such primate research continues to facilitate insights into both novel pharmacological therapies, and more recently established drug treatments like dopamine agonists.[48–50]

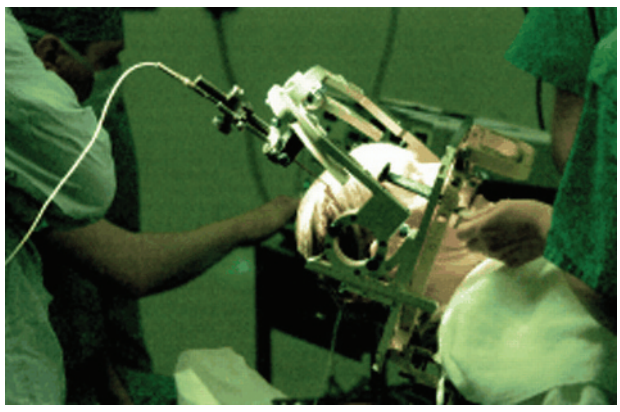

Figure 3 Intraoperative deep brain stimulation for Parkinson's disease.

FUTURE

Therapeutic prospects

The progress of several exciting therapeutic prospects for PD has been driven by advances made first in cellular in vitro studies, then non-primate mammalian research and ultimately by refinement in primate models. Notable treatments in which clinical trials have recently been undertaken include neural transplantation and gene therapy for PD.

Neural transplantation aims to replace the neurons that release the neurotransmitter dopamine and connect the substantia nigra and the striatum of the basal ganglia that degenerate in PD. The many donor cell sources under consideration include porcine neural xenografts, human fetal tissue, and human stem cells. However, several clinical trials have recently generated controversies, many centred on the development of dyskinesias after transplantation.[51 52] These dyskinesias are postulated to arise from changed dopamine release but the mechanisms remain contentious and some have suggested that they may only occur in certain subgroups of patients.[53] The clinical experience of neural transplantation underlines how essential it is to conduct appropriate preclinical experiments and evaluate them properly before entering clinical trials. Primate research has shown itself to be essential to progress in this regard.[54 55]

Primate models have been vital to the development of gene therapy for PD. Current clinical trials of gene therapy aim to replace either γ-aminobutyric acid (GABA), a neurotransmitter released from neurons with inputs to several basal ganglia structures, or to insert glial cell line derived neurotrophic factor (GDNF) to arrest and even reverse the degeneration of nigrostriatal neurons in the basal ganglia. Alongside constant infusions of recombinant factors, the use of viral vectors is widely considered to be the most efficient, practical, and safe method to deliver gene therapy to basal ganglia structures at present. In theory, viral vectors also confer the advantage of requiring only a single treatment. Furthermore, it is suggested that neurotrophic gene therapy is in principle less likely to cause unwanted dyskinesias as it restores the patient's own neural function, rather than replacing it as neural grafts aim to do. The consensus is that primate research is best positioned to confirm both that gene therapy is safe and that its functional restoration is lasting.[56]

One promising form of gene therapy using viral vectors that may soon reach clinical trials entails the introduction of enzymes required for dopamine synthesis into the striatum of the basal ganglia. This method has had great success in restoring motor function in a 6-OHDA rodent model of parkinsonism.[57] However, if anything is to be learnt from the controversies surrounding clinical trials of neural transplantation for PD, it is that such a treatment must be validated by primate research. In particular, only robust demonstration of

Box 1 The three Rs

- Reduce the number of animals used to a minimum
- Refine the way experiments are carried out, to make sure animals suffer as little as possible
- Replace animal experiments with non-animal techniques wherever possible

Box 2 Key points

- Primate research has contributed greatly to our understanding of the pathophysiology of Parkinson's disease and other movement disorders.
- Established medical treatments for Parkinson's disease like dopamine agonist therapy continue to require animal models to assess their efficacy, safety, and mechanism of action.
- Recently developed treatments for Parkinson's disease such as deep brain stimulation of the subthalamic nucleus required validation of their safety and efficacy in primate models before progression to clinical trials.
- Controversies surrounding potential treatments for Parkinson's disease like fetal cell transplantation demonstrate the need for properly evaluated preclinical research using appropriate animal models before progression to clinical trials.
- Primates and other animals should not be used in scientific research without adherence to the three Rs of humane technique enshrined in UK legislation.

efficacy and safety in the MPTP primate model of PD will enable clinical trials of this treatment to be considered.

As a caveat, amid all the excitement surrounding future treatments for PD it has recently been argued that merely attempting to restore dopamine release from the nigrostriatal neurons of the basal ganglia will remain limited in the extent to which it addresses the problems caused by PD. Thus, shifts of research focus may be preferable, firstly towards halting disease progression,[58] and secondly towards understanding its aetiology with a view to disease prevention. As the best models of PD are currently primate models, they will continue to be crucial, both to characterising factors related to the onset and progression of neuronal degeneration in the parkinsonian brain, and in the development of preventative strategies.[59]

DISCUSSION

Much has been learnt about PD and other movement disorders from studies of cells in culture, rodents, and other animal models. Nevertheless, alongside empirical observations in patients and serendipitous clinical discoveries, the most valuable advances have been made because of the availability of accurate disease models in species whose nervous systems emulate the size and complexity of the human nervous system. Primates are the only non-human animals that are bipedal making them unique in the study of movement disorders. They are also the only animals dexterous enough to perform the delicate motor tasks required to evaluate properly their motor function in models of PD. Moreover, the MPTP and 6-OHDA primate models of PD remain the only experimental models to reproduce faithfully the TRAP signs of PD. Thus, research involving primates has been instrumental to many of the advances made in our understanding of PD and its treatment. In particular, the example of DBS of the subthalamic nucleus for PD demonstrates a therapy whereby primate research has not only been essential to advancing our theoretical framework, but also provided evidence to justify clinical trials in patients leading to successful treatments.

It has recently been claimed that by the standards of modern evidence based medicine there is little evidence that animal research benefits humans.[60] The spuriousness of such an argument has been highlighted elsewhere, emphasising

Box 3 Key papers

Preclinical

- Aziz TZ, Peggs D, Sambrook MA, *et al*. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Mov Disord* 1991;**6**:288–92.
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Clinical

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Box 4 Useful web sites

- PD SURG Trial http://www.pdsurg.bham.ac.uk
- Research Defence Society http://www.rds-online.org.uk
- The Boyd Group http://www.boyd-group.demon.co.uk
- The Parkinson's Appeal http://www.parkinsonsappeal.com

that animal research is at present best evaluated by qualitative critical reviews rather than quantitative systematic reviews that inappropriately apply methodology designed for the analysis of clinical trials.[61 62]

Primates and other animals should not be used in scientific research without careful consideration of the necessity of the research undertaken and adherence to the ''three Rs'' of humane technique that are advocated by the Research Defence Society (http://www.rds-online.org.uk) and enshrined in UK legislation (see box 1).[63] Best practice is for animal experiments to occur in conjunction with clinical research in patients, by clinician scientists and basic scientists collaborating with clinicians, to increase its effectiveness and applicability to the human condition. The development of methods to survey the literature of primate research and the funding of initiatives to evaluate its utility and clinical need, like the non-human primate study (http://www.nhpstudy.com), are worthy and important endeavours.

CONCLUSIONS

This review shows for PD that many of the fruits of research involving primates have been substantiated in clinical practice. Research on primates has played—and continues to play—a crucial part in deepening our understanding of the brain. Such research has been indispensable to the advancement of our understanding of PD pathophysiology, and continues to be invaluable to improving current therapies and developing new treatments for PD that are both safe and effective. In conducting animal research, the three Rs of humane technique—reduction, refinement and replacement—should be adhered to.

MUTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. The following are causes of parkinsonism.

(A) hydrocephalus
(B) HIV
(C) trauma
(D) smoking
(E) encephalitis

2. The following signs are present in Parkinson's disease.

(A) bradykinesia
(B) rigidity
(C) athetosis
(D) resting tremor
(E) pronator drift

3. The following animal based experimental paradigms directly advanced our understanding of Parkinson's disease.

(A) Burns *et al*'s MPTP lesioned primates
(B) Fulton's frontally lobotomised primates
(C) Kluver and Bucy's temporally lobectomised primates
(D) Sherrington's decerebrate cats and primates
(E) Horsley and Clarke's animal stereotaxis

4. Future therapeutic prospects for Parkinson's disease actively researched in primates include.

(A) Stem cell therapy to restore dopamine depleted basal ganglia structures
(B) Gene therapy to restore GABA neurotransmission in the basal ganglia
(C) Adrenal cortex transplantation to replace dopamine depleted basal ganglia structures
(D) Deep brain stimulation of the pedunculopontine nucleus
(E) Nanotechnology implantation to restore damaged basal ganglia structures

5. The following Rs are principles of animal research explicitly advocated by the Research Defence Society.

(A) Replacement of animal experiments with alternatives wherever possible
(B) Realism to conduct experiments that yield clinically applicable results
(C) Refinement of experiments to minimise animal suffering
(D) Reduction of animal experiments to a minimum
(E) Respectability of scientists conducting experiments

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ANSWERS

(A) T, (B) T, (C) T, (D) F, (E) T; 2. (A) T, (B) T, (C) F, (D) T, (E) F; 3. (A) T, (B) T, (C) F, (D) T, (E) T; 4. (A) T, (B) T, (C) F, (D) T, (E) F; 5. (A) T, (B) F, (C) T, (D) T, (E) F.