The Edinburgh Parkinson's Lecture 2017

The quest to find a cure for Parkinson's disease
Mentored by a Madman: The William Burroughs experiment

Professor Andrew Lees MD, FRCP, FMedSci

Report on the talk prepared by Helen Harris, Edinburgh Branch Volunteer
(explanations of some terms are given at the end)

Welcome and Introduction

All were welcomed by **Dr. Conor Maguire** as Director of Education at the Royal College of Physicians of Edinburgh which holds over 60,000 books in its vaults. The College archives include a first edition of *The Shaking Palsy* essay by James Parkinson, currently on display for all to see. To mark the 200th anniversary of the essay's publication, the evening's lecture was being followed by a two-day multi-disciplinary conference entitled "Parkinson's Disease 200: Back to the Future."

Professor Siddarthan Chandran was particularly delighted to introduce Professor Lees, a teacher and mentor during part of his training as a neurologist. He acknowledged Professor Lees' international recognition for outstanding work in Parkinson's Disease (PD), his key role in establishing the Queen Square Brain Bank for Neurological Disorders, his enormous influence in establishing criteria for the observation and diagnosis of PD, as well as the use of apomorphine to help manage the condition. What was also remarkable was Lees' position as the most cited researcher in PD and particularly so for someone who had spent most of his career as a "jobbing" NHS neurologist while having a research focus. However, he felt it was Lees' extra-curricular activities that had led him to the topic of this evening's lecture which was also the title of his recently published memoir.

The Lecture

Setting the Scene

"What would James Parkinson himself think if he were alive today?" Lees believed he would be very disappointed because we still haven't found a way of stopping PD. There has been no magic moment since L-dopa became available in the 1960's. Lees was one of the first junior doctors in England who had the privilege to use the drug and witness the profound beneficial effects on patients severely incapacitated by PD. It was these experiences that initiated his career-long interest in the condition. At the time, the medical profession thought that within 10 years they would have found the answers for Alzheimer's, motor neurone disease and PD, but it was not to be. What Lees sought to do with his presentation was to draw our attention to likely contributing factors for the lack of success and concerning modes of doctoring and approaches to medical research over the last 50 years. That said, he was hopeful about the future because we now have 'neurophiliacs' (those fascinated with neuroscience) whom he also referred to as Oliver Sachs[1] groupies, as well as young medical students more revolutionary than previous generations. Some have been taking notice of what he has to say in his memoir which he preferred to call his **emanation**.

Becoming a Doctor

Throughout his career, fundamental to Lees' approach, has been **recognition of his patients as his teachers**. They have also stimulated most of his research. His training at the Royal London Hospital was in the tradition of the Canadian physician, William Osler with his dictum,

> *"The good physician treats the disease, the great physician treats the patient who has the disease."*

and the type of doctoring expressed in W H Auden's poem

> *Give me a doctor partridge-plump,*
> *Short in the leg and broad in the rump,*
> *An endomorph with gentle hands*
> *Who'll never make absurd demands*
> *That I abandon all my vices*
> *Nor pull a long face in a crisis,*
> *But with a twinkle in his eye*
> *Will tell me that I have to die.*

Lees believes that doctors are not scientists but artists and within their job description there is a conflict because, not only do they need to give pastoral care, especially within the field of neurology with its brutal and incurable diseases, they should devote some time to research which needs a different mind-set. In recent decades this has led to **polarisation between science and good doctoring which will prove a significant problem if not addressed**.

Specialising in Neurology

Lees had two remarkable teachers at University College Hospital. Gerald Stern taught him that **uncertainties and mistakes are an inevitable part of medicine** even in a risk-averse society – it is how we learn and there should be a facility to admit mistakes. William Gooddy advised Lees to **spend time at patients bedsides listening** to what they say AND to read Conan Doyle's *The Complete Works of Sherlock Holmes* as well as Marcel Proust's *À la Recherche du Temps Perdu* (*Remembrance of Things Past* or *In Search of Lost Time*). Lees didn't get around to reading Proust till much later in his career but when he did he realised what he had to offer stemmed from his attendance with many neurologists in Paris (Proust suffered from asthma, then regarded as a neurological condition). Lees recommended **anyone interested in memory to read Proust** (Gooddy had probably recommended him because of his own fascination with time).

Lees did immediately take up the suggestion of reading Sherlock Holmes. The message here was the importance of giving reasons in solving a crime based on Holmes' considerable powers of observation and deduction. Lees later realised this was Gooddy's way of introducing him to William Gowers (1845-1915), subsequently Lees' hero. Gowers used similar methods to Holmes emphasising **the importance of observation and eliciting precise information**. Lees has tried to observe these principles throughout his time on the wards at UCLH and the National Hospital, Queen Square.

Lees demonstrated the importance of observation with a video of the 20 sec. **finger-tapping test** performed by someone with PSP (Progressive Supranuclear Palsy) and another with

PD. With the former, the tapping is at a normal speed but the amplitude is small and consistently so, whereas with the PD patient, the amplitude and the speed of movement rapidly diminish. Yet this had not previously been observed by neurologists until Lees and his associates pointed it out in a paper published in 2012.

Another example relating to observation concerned **Ray Kennedy**, a highly acclaimed Arsenal, Liverpool and England footballer in the 1970s and early 1980s, who was diagnosed with PD at the age of 35. Lees was Kennedy's neurologist. Athletes are great self-observers, being acutely aware of their bodies. With hindsight, Kennedy realised that some of his personal observations from 10 years before his diagnosis were probably early symptoms of PD. Lees paid very close attention to Kennedy and felt he had probably learned more from observing and treating him than any other of his PD patients. Lees ultimately co-authored *Ray of Hope: The Ray Kennedy Story*. With enormous difficulty Lees finally managed to get a paper published in the Movement Disorder Journal [in 1992] about his observations with Kennedy. What ultimately emerged is now a multi-billion dollar research industry looking at prediagnostic PD to work out when the disease kicks in, even though there are no typical signs and symptoms Lees bemoaned the fact that it is **now very difficult to get case reports published yet they still play an important role** and editors of journals should be ashamed they don't take them. Instead they chase impact factors[2].

<u>Becoming a Researcher</u>

When Lees was a 6th former he watched the TV programme "Your Life in their Hands." In one episode they showed a patient with a bad tremor being operated on with a new procedure involving a probe into the brain and called a thalamotomy. It was spectacularly successful at getting rid of the tremor. [Thalamotomy destroys part of the thalamus, Deep Brain Stimulation is a less destructive alternative today]. Lees believes the programme and his experience with L-dopa influenced the path he ultimately took with his research focus on PD.

<u>Influence of William Burroughs</u>[3]

Lees first read Burroughs book, *Naked Lunch*[4] during a period of disaffection with his early medical training. It was the front cover of the Beatles LP *Sergeant Pepper's Lonely Hearts Club Band* that first brought Burroughs into view (second row next to Marilyn Monroe). He looked him up and learned of *Naked Lunch*. Lees got hold of a copy and read about Dr. Benway, a character in the book and the antithesis of what a good doctor should be. Benway resonated with him because of some of his surgical teachers at the time. The disaffection melted and Lees set aside his interest in Burroughs till much later when he was well into research. He summed up the ultimate influence of Burroughs on his research with a quote from his memoir/emanation.

> *"He reminded me to be open-minded and non-judgemental and run with what life threw my way. He emphasised I should never miss a chance. He looked at the literature in a slanted and unusual way. He showed me that dead ends were part of scientific research and that I should never rule anything out. He had taught me that I had the capacity to work miracles but at the same time I needed to be highly sceptical. He taught me that egotism and single-mindedness were prerequisites for research and that science had always followed Jesus not Marx. He encouraged me to get away from concrete thinking,*

float in outer space and to run alongside a beam of light. He also reminded me that clinical investigation should not be limited to institutions and that scientists must find new ways to regain the power to explore."

Constraints Impacting Research

Burroughs railed against the misbehaviour of the pharmaceutical industry, the development of me-too drugs[5] and putting profitability over patients but he was equally critical about the medical profession and universities in relation to research. Lees believes the **regulation of clinical research is now extraordinarily bureaucratic, expensive and confusing and destructive to progress** and that **over-regulation may lead to serious bias in clinical research and restrict it to large organisations**. The mega industry *surrounding* research rather than *doing* it is that the "medical mavericks" are being driven out of medical research to the detriment of society. These have included people like Patrick Steptoe who pioneered IVF, John Charnley who pioneered the hip replacement operation and Barry Marshall who had to swallow a petri dish of *Helicobacter pylori* before anyone would believe the bacterium could survive in the stomach [and had a causal link to acute gastritis and peptic ulcers and more recently gastric cancers].

Why haven't we had a better treatment than L-dopa? Some of the reasons Lees feels are: a) the pharmaceutical industry has moved too much toward **theory driven drug design**; b) a **serious reduction in the time research clinicians see patients**; c) **constriction in the range of compounds tested** influenced by growing risk aversion in society; and d) **too much emphasis on double-blind placebo control trials** at the expense of observational studies. Lees was able to do so much more in the 80's than he can do now with his research.

Work with Apomorphine

Burroughs, who was hooked on narcotics, came to London in desperation in the 80's and was treated by a private physician, John Dent for drug addiction with what Burroughs called a junk vaccine, apomorphine (it had to be injected). It made people vomit but Dent believed it wasn't because the drug made people sick that got them off narcotics but its metabolic effects on the hind brain. Burroughs stayed off narcotics for several years as a result and became a champion of apomorphine. He encouraged research into similar alternatives that wouldn't have to be injected or make people vomit. No-one took much notice. In the late 80's Lees and others began to witness the on-off syndrome with PD patients who had been on L-dopa for years. Lees looked around for new treatments to help. Burroughs experience with apomorphine came to mind because by now it was realised the compound was a powerful stimulator of dopaminergic systems.

Lees tracked down a supply and injected himself – the appropriate thing to do at the time – with no negative consequences. Nowadays **self-experimentation** is rejected by universities. It's seen as being biased and irrelevant to patients. Even if you manage to get ethical approval from a university, very few journals will accept it, so this approach has gone underground, especially in the psychiatric field.

After approval by the hospital ethics committee, Lees and his colleagues treated 20 patients with apomorphine together with domperidone (to counteract the vomiting) and ultimately had a paper reporting the trial accepted by *The Lancet* – it would be laughed out of court if

submitted now. Lees and Stern then went down to the Medicines Agency at the Elephant & Castle, showed them a video of the trial patients improvements. Because the Agency had much information about apomorphine's safety, being an old drug, they granted a licence. The drug is now in the NICE guidelines and is used in many countries for the treatment of PD. Today such a process would take at least 10 years.

Now that Lees has more time (being in the autumn of his career) he made contact with a colleague from the 1970's, John Neumeyer, a medicinal chemist in the psychiatric hospital at Harvard. Neumeyer has been making apomorphine-like drugs for 20 years but not a single pharmaceutical company has approached him, despite the fact that apomorphine is known to be one of the most potent dopamine agonists ever discovered. With legacy money Lees has been able to do some work with marmosets using a drug, MPTP, to induce Parkinsonism – the marmosets then don't move. Via a video Lees showed how with one of Neumeyer's compounds administered orally, within 10 mins the marmosets began to move freely. Britannia Pharmaceuticals who make and market apomorphine have now agreed to buy patents for some of Neumeyer's compounds and taken them into pre-clinical development. Lees is hopeful that this will result in a powerful oral dopamine agonist that doesn't cause impulse control disorders going into clinical trial next year.

L-dopa Addiction

Another of Burroughs influences on Lees research has been in the area of **Dopamine Dysregulation Syndrome**. In 2000 a patient's wife told Lees of her husband's addiction to L-dopa, which Lees didn't at first believe. Then others came along and within a year Lees and his associates had identified 15 patients with the behaviour. It is not the usual compulsive behaviour associated with PD treatment but a craving and wanting, not a liking, for the drug, with patients requesting higher and higher doses and even creating secret L-dopa stashes. It is not common, appearing in about 0.5% of patients, usually men.

Lees first presented his experience at a conference in Chicago. Many did not accept the idea but eventually he received help from psychologists and gradually existence of the syndrome has become accepted. Lees needed to try and understand addiction and began to read the literature but struggled to understand it. He returned to Burroughs' works including his first book, *Junky*, and realised Burroughs had anticipated what is now being recognised as a metabolic disorder in which the brain is altered.

The outcome is that Lees is now collaborating in pleasure-and-reward experiments. He showed a video of a PD patient with a hand tremor, sorting cards and being rewarded with money if he put a card on the correct pile. The reward exercise reduced the patient's hand tremor and speeded up his movements. Lees hopes that we can drive the reward system in a more consistent way to help in the treatment of PD. All this stems from an unwanted complication in a small number of patients. Pertinent to the reward system is the fashionable interest in the benefits of exercise, tai chi, dance etc for people with PD – these are reward generating activities.

In conclusion

Lees believes that real progress in finding better treatments is now being made in different areas. He also suggests that serendipity is important – we need to keep our eyes open, listen and then act on what we might see by chance. To him the **altamirage** effect [good luck prompted as a result of personally distinctive actions] is a key component of research which can happen by bringing your hobbies and interests into your work and using the interplay between them. For Lees it was his fascination with the writings of William Burroughs.

Finally, Lees finished with profound words attributed to Gautama Buddha, ca. 500BC

> *"Do not accept what you hear by report, do not accept tradition, do not accept a statement because it is found in our books, nor because it is in accord with your belief, nor because it is the saying of your teacher. Be lamps unto yourselves."*

Summary of Responses by Lees to Questions from the Audience:

1) Lees felt that we should pay more attention to the level of risk people are prepared to take. Those who decide *what* risks to take are not usually the patients. He suggested there is scope for academics working outside universities with patient groups.

2) The drugs included in the NICE Guidelines for the treatment of PD mysteriously disappear, with patients unable to obtain them. Some patients are given a different L-dopa formulation every time they go to the pharmacy, which Lees regards as a major scandal, given the critical aspect of L-dopa bioavailability. Katherine Crawford for P-UK stated that as a charity P-UK are keen to hear about such instances.

3) We need to work on identifying the difference between the everyday stresses that can make PD symptoms worse and the stresses/stimuli that can override PD symptoms, such as escaping from a fire and perhaps doing so faster than someone without PD.

4) Because of the lack of disease modifying treatment at the moment there's no pressure on doctors to make a very early diagnosis and such diagnosis may in fact be damaging for the patient. It's important from a research perspective but what is important from the patient's perspective is *timely diagnosis* i.e. once the condition is causing a range of problems.

5) There's scope for exploring more as to why music helps in the movement disorders associated with PD. Lees cited the example of one of his patients who has no movement restrictions while dancing at a discotheque

Closing Remarks from Katherine Crawford, Director of Support and Local Networks, Parkinson's UK

Katherine Crawford thanked Professor Lees for his erudite exposition through his life journey as a neurologist specialising in PD then asked what can we do in the quest to find a cure? The emphasis on looking and listening and the person-centred approach described by Professor Lees resonates with P-UK objectives. The voice that we have is as important as it ever has been in helping all those involved in seeking a cure for PD.

Some Explanations/Background

1. Oliver Sacks (1933-2015) was a neurologist, naturalist, science historian and applauded author who was born, educated and trained in the UK but who spent his career in the USA. His books were essentially based on detailed case histories of people with neurological disorders and of his own ailments. Some were adapted into feature films, documentaries, plays and an opera. The most well-known work is probably “The Man Who Mistook his Wife for a Hat.”

2. The impact factor (IF) or journal impact factor (JIF) of an academic journal is a measure reflecting the yearly average number of citations to recent articles published in that journal. (Ex: Wikipedia.)

3. William Burroughs (1914-1997) was a founder of the Beat Movement – an artistic outpouring of non-traditional free expression. He was a satirist writer, renowned for his startling and semi-autobiographical accounts of drug culture. He became a heroin addict. *Junky* was his first book.

4. In *Naked Lunch*, Burroughs third book, published in 1962, he exposes the pitfalls of America's consumerist state and the overall human addiction to control. Its sub-plots of taboo fantasies and drug-addiction, peculiar and monstrous creatures, eccentric personalities and corruption help unmask mechanisms and processes of control. It led to much controversy among American readers. (Ex: Wikipedia)

5. A drug that is structurally very similar to already known drugs, with only minor differences. The term "me-too" carries a negative connotation. (Ex: Medicinenet.com)
