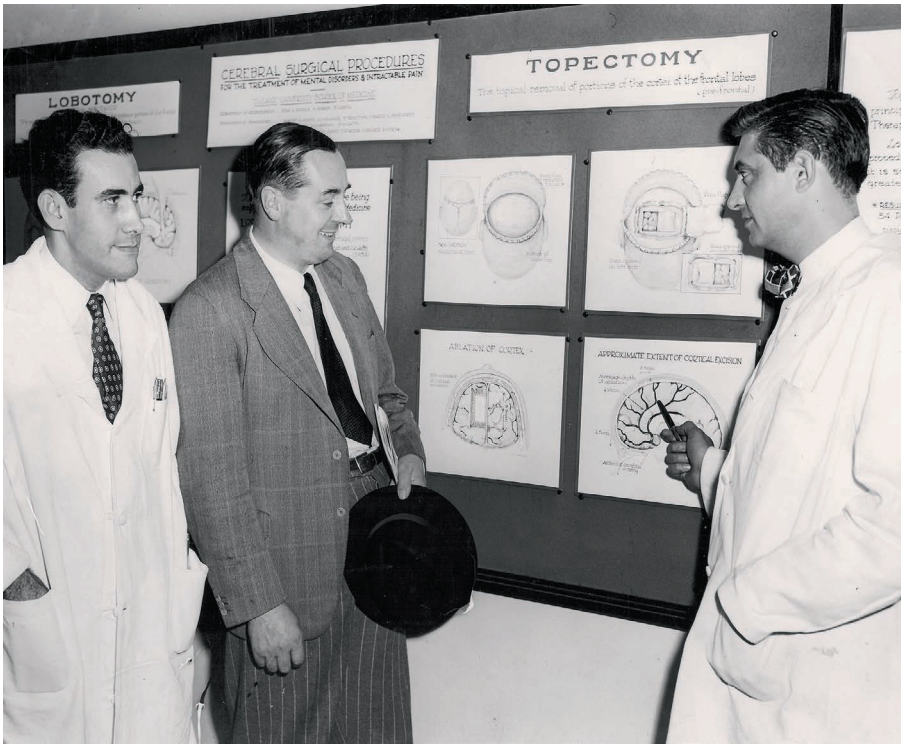

Robert Heath, far right, conducted experiments with brain stimulation.

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NEUROSCIENCE

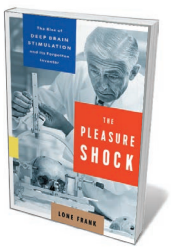
Pulse of the past

Christian Lüscher considers an alarming account of the early days of deep-brain stimulation.

Many people consider deep-brain stimulation (DBS) to have begun in 1987 in Grenoble, France, when Pierre Pollak and Alim Benabid stopped a person's tremor by delivering high-frequency pulses of electricity to her thalamus. In fact, more than three decades earlier, a psychiatrist called Robert G. Heath at Tulane University in New Orleans, Louisiana, had experimented with this approach. Now, science writer Lone Frank pulls Heath (1915–99) from obscurity for her exploration of DBS, *The Pleasure Shock*.

Frank has traced and interviewed surviving patients, former collaborators, family members and current DBS scientists. The result is a rarity: a thrilling, well-researched read. Above all, it is a chilling reminder of how early neurosurgical experimentation knew few ethical boundaries — even firmly within the medical and academic establishment. Heath was chair of Tulane's psychiatry and neurology department for 31 years, from 1949 to 1980.

Today, DBS is an approved treatment for Parkinson's disease, dystonia (uncontrollable muscle contractions) and essential tremor. Other indications, such as therapy for obsessive–compulsive disorder, depression and addiction, are the focus of intensive research. Just a few patients are treated 'off label', with mixed results.



The Pleasure Shock: The Rise of Deep Brain Stimulation and Its Forgotten Inventor
LONE FRANK
Dutton: 2018.

Heath explored the effects of electrical stimulation on various people, with and without their informed consent. Infamously, in the 1970s he subjected a homosexual man to DBS — for so-called 'conversion therapy', the now-discredited practice of attempting to alter sexual preference. Heath delivered pulses to the septal region of the man's brain (normally active during pleasure), and showed him pornographic material featuring women. Heath obtained permission from a state court to pay a woman to perform sexual acts with the man, while recording activity in his septum. Heath claimed that the man became heterosexual; this was later contested.

As early as the 1950s, Heath also implanted electrodes in people with schizophrenia, violent behaviour and depression. Towards the end of his career, he proposed stimulation of the cerebellum for the treatment of epilepsy, which he thought was closely related to schizophrenia.

Frank paints a detailed picture of the staggering ethical vacuum in which this egregious research was conducted. This was the period after the rise and fall of prefrontal lobotomies, from the 1940s to the 1950s. It was also when chlorpromazine was introduced as the first drug for psychosis. Several of the people Heath experimented on experienced post-operative complications, and contemporaries raised serious questions in the literature of the time about his methods and conclusions. All of this makes Heath's long and troubling career a useful subject of study, because it illustrates the beginnings of biological psychiatry.

A strength of the book stems from the parallels that Frank draws with current brain research, notwithstanding today's dramatically different protections for the dignity, rights and welfare of research participants. For example, Frank compares Heath's involvement in the CIA's mind-control experiment MKUltra, which ran from the 1950s to the 1970s, with the current DBS initiative led by the Defence Advanced Research Project Agency, which aims to understand the workings of the brain. The comparison might not please everyone, but it underlines the need for a debate on the independence of research in psychiatry.

Beyond DBS, Heath tested pharmacological substances such as bulbocapnine, which induces therapeutic stupor, on inmates of the Louisiana State Penitentiary at Angola, in the context of MKUltra. Sadly, he was not alone in using prisoners for medical research; from the 1940s to the 1960s, covert testing of drugs, radioactive substances and more was carried out on many people powerless to refuse.

Heath also propounded the idea that a component that he called taraxein, isolated from the blood serum of people with schizophrenia, would elicit symptoms in healthy people. The prisoners he injected quickly learned to perform what he expected them to, for example acting out hallucinations. The episode encapsulates both the alarming ethical mores of the day and why observations need to be made under blinded conditions.

There are a few gaps. Frank talked to many DBS experts, but not to Pollak or Benabid, who pioneered the most important use of the technique today, in the subthalamic nucleus. I also wanted to know whether Heath knew of the Nobel-prizewinning work of physiologist Walter Rudolf Hess on

cats' emotional reaction to electrical brain stimulation, carried out in the 1930s. That evidence could have been a stimulus for Heath's experiments in humans. Some anatomical schematics could have helped the non-expert; and I wished for photographs of Heath at work.

Was Heath an out-and-out monster or a deeply flawed visionary? Frank does not shy away from that question. She vividly describes his charismatic, take-charge personality, analysing his work in the context of his time. He called his house outside New Orleans Hedonia (meaning pleasure); hosted lavish parties; and was a gifted tennis player, all of which probably contributed to his social success in the American deep south of the mid-twentieth century. Frank also makes it clear that much of Heath's research — and the academic environment that allowed it — was appalling.

Today, little remains of Heath's science, in part because he did not systematically investigate underlying mechanisms. In the absence of a demonstration of what causes a condition, it is difficult to propose a stimulation protocol that works. When DBS is used for Parkinson's disease, we know that high-frequency stimulation in the subthalamic nucleus alleviates symptoms, even though the underlying cellular mechanism is debated.

"Contemporaries raised serious questions in the literature of the time about his methods and conclusions."

The future of DBS seems bright thanks to optogenetics, the use of light to control the activity of cells. Over the past decade, scientists have teased apart neural dysfunction in animal models of behavioural conditions such as obsessive–compulsive disorder or addiction. New DBS protocols are currently tested in such models. Treatments likely to reach clinics over the few next years are inspired by optogenetic manipulations of cellular mechanisms to restore normal function in specific brain regions.

The main message of Frank's fascinating, horrifying tale is that progress can be made only through research that is scrupulously ethical. Luckily for the patients of today and tomorrow, DBS got a second chance when it was reinvented in 1987. ■

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GENETICS

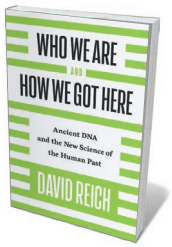
Traces of ancient DNA

Turi King hails David Reich's thrilling account of mapping humans through time and place.

As a field, ancient DNA is paradoxically young — just over 30 years old. And it is booming, thanks to ever-faster sequencing techniques and extraction protocols that can bait specific sections of human DNA out of the vast soup of non-human genetic material in ancient samples. Simultaneously, the field has grabbed the public imagination with findings about the distant past. One such finding was the revelation that people from the Beaker Culture significantly altered Britain's population just 4,500 years ago. Another was the oldest ancient genome ever obtained: that of a 700,000-year-old horse, found in Canadian permafrost, that suggested the ancestor of all today's horses, donkeys and zebras lived some 4 million years ago. I was thrown headlong into the intricacies and difficulties of the field by leading the DNA analysis of the remains of England's King Richard III, discovered under a car park in Leicester in 2012.

Few labs do ancient-DNA work. David Reich's, set up in 2013 at Harvard Medical School in Boston, Massachusetts, was the first in the United States and is one of the most prestigious in the world. It is a juggernaut able to process hundreds of samples a year. Now, with *Who We Are and How We Got Here*, Reich gives us a window into what ancient DNA can tell us about human evolution, the peopling of the world, continent by continent, and the population mixing that makes us who we are today, genetically at least.

Reich's team has developed some of the most sophisticated statistical and bioinformatics techniques available. Using computers, they painstakingly reconstruct genomic information from fragments of DNA from ancient individuals. They then drill down in search of a new understanding of human history.



Who We Are and How We Got Here: Ancient DNA and the New Science of the Human Past
DAVID REICH
Pantheon: 2018.

It was Reich's lab that did the Beaker work of the headlines. Indeed, the group has been involved in many of the big findings in the field over the past decade, and it's these that Reich discusses. For example, their work contributed to the startling discovery that Neanderthals interbred with the ancestors of all modern humans descended from Europeans, Asians and other non-Africans.

His group's involvement in the genetic analysis of the hominins called Denisovans overturned previous findings based on mitochondrial DNA alone. The work showed that Denisovans and Neanderthals were more closely related to each other than to modern humans. The ancestral groups leading to modern humans separated from the population leading to both Denisovans and Neanderthals 770,000–550,000 years ago, pre-dating by some 100,000–400,000 years the split that led to Neanderthals and Denisovans. And it turned out that ancient Denisovan populations and the ancestors of modern New Guineans had interbred as recently as 54,000–44,000 years ago.

Reich also discusses ghosts in our past. Not all of the genetic make-up of ancient and modern humans can be explained by the current archaeological or historical record. Genetic analysis of ancient and modern populations predicts as-yet-undiscovered groups that must have contributed their DNA to future generations. For example, Reich's lab found that Europeans were more closely related to Native Americans than to East Asians, and this couldn't be explained by recent interbreeding. The researchers suggested that another, now-extinct, group of people must have existed more than 15,000 years ago, and contributed DNA both to the populations that led to ▶

NIKOLA SOLIC/REUTERS

A replica Neanderthal skull.