Chapter 11 Another Chapter?

On May 1, 2000, a further chapter in the history of the shock therapies opened. Katherine E, a 20-year-old girl, was wheeled into a specially prepared room in the university psychiatric clinic in Berne, Switzerland, where she was put to sleep in the way patients have been put to sleep for ECT for decades. But instead of being given ECT, she had a magnetic paddle placed in close proximity to her skull and with the stimulus delivered in this way she went on to have a seizure. The team looking after her, Thomas Schlaepfer and Holly Lisanby, were mightily relieved that the seizure happened uneventfully. And there was a pleasant surprise in store for them. When she awoke Katherine appeared to have less confusion than sometimes accompanies recovery from ECT. She had three further magnetically induced seizures before finishing her treatment course with conventional ECT, and during these three further magnetic treatments the beneficial cognitive profile of the new treatment appeared to be maintained.[1] Magnetic Seizure Therapy (MST) had been borne – or had it?

Katherine had previously been treated with eight different courses of antidepressant drugs with no success. In many countries, despite her age, she would have been a candidate for ECT. In Switzerland, however, the idea of giving her ECT was relatively novel. Up to the few years beforehand ECT had all but been banned. Tom Schlaepfer and a small group of younger clinicians had been instrumental in effectively re-introducing it, portraying modern ECT as a treatment, in which the writhing of patients was abolished by suxamethonium, and the convulsive process was monitored scientifically by simultaneous EEG recording. Schlaepfer had gone as far as bringing patients' relatives or their advocates and antipsychiatry critics of ECT into the treatment suite to monitor what happened. And there they saw a treatment that much more closely resembled a standard surgical procedure than the stuff of Cuckoo Nest fantasy.

Re-introducing ECT, however, was not something that had to be sanctioned by an ethics committee. An entirely novel treatment, such as magnetic seizure therapy, would have to be approved by such a committee. Schlaepfer had brought his proposals before the Berne Institutional Review Board and had been knocked back twice. He, Harold Sackeim and Holly Lisanby, were aiming at a proof of concept – demonstrating that a seizure could be safely induced in this way. Their plan was to administer the treatment to four patients, who would each begin a course of convulsive therapy with magnetically induced seizures and finish out their treatment with a proven therapy – ECT. The Berne ethics committee had serious problems with this – wondering what image Schlaepfer and his colleagues must have of human beings if they were prepared to treat people this way. On the third attempt, the new procedure passed. But this was not simply a case of Berne conservatism holding back science; the reason to go to Berne was that Sackeim, Lisanby and Schlaepfer recognized that there was even less likelihood that Columbia University, Sackeim and Lisanby's parent institution, would pass a protocol for the new treatment.[2]

Following treatment as of the time of writing, Katherine had not had any relapse of her illness and was drug free. MST was given to three more patients in Berne and has since been given to a further 20 patients in America with broadly speaking similar results.[3]

Patients appear to do relatively well and, according to the advocates of the treatment, its cognitive complications appear quite benign. For some, this has raised the possibility that MST might be a replacement for ECT.

But if we pull our focus back from the figure of Katherine to take in the room in which she had treatment, the picture becomes more complex. The suite was specially adapted for the purposes of treatment. Huge orange power cables had to be engineered into the room to feed the magnetic capacitor that delivered the treatment. One estimate was that the amount of power involved would have supplied the needs of two typical Manhattan blocks. So if magnetic seizure therapy were ever to replace ECT, it would at the very least have to wait on technological developments. And even then there still remains the question as to whether it works. It is clearly possible to induce a seizure magnetically – there had in fact been little reason to doubt this, but these seizures are triggered in regions of the cortex near to the surface of the brain and it is not yet clear that seizures initiated in this way will bring about changes in whatever key brain areas mediate the beneficial effects of ECT. Since Jan-Otto Ottosson's work in the 1960s it has been a clinical truism that not all seizures are equivalent.[4]

Transcranial magnetic stimulation

The developments that brought Katherine to a room in Berne had begun some 25 years earlier in Sheffield, England, and then picked up pace 15 years previously. While engaged in his doctoral thesis in the mid-1970s, Tony Barker had come to the conclusion that there might be some benefit in altering human electrical fields with magnetic stimulation.[5] Barker needed to selectively stimulate fibres within a peripheral nerve. Peripheral nerves carry both fast and slow fibres. The fast fibres carry reflex motor actions, while the slow fibres carry sensations like pain and heat. These have different thresholds of stimulation, so in principle it should be possible to stimulate one set of fibres and not the other. But electrical stimulation applied to the surface of the arms or to the skull activates both fast and slow fibres. It was almost impossible to get selective results with an applied electric field.

Magnetic fields were an alternative and in 1982, after getting his PhD, Tony Barker returned to the topic, which was to selectively stimulate fast nerves while leaving slow nerves untouched. Using a magnetic coil applied to the nerves in the arm, he was able to do just this.[6] The next question was: could the same be done for the brain. Coming to the problem as an engineer rather than a biologist or a physician, this project seemed to have potential pitfalls to Barker. Could magnetic stimulation of the brain wipe out memory, or otherwise interfere with important intimate functions and perhaps do so permanently? Barker was unaware of the precedent of ECT. He was also unaware that 80 years earlier a number of less cautious experimenters had put their heads inside large magnetic coils and reported that switching the coils on could induce phosphenes and other indications of brain stimulation.[7]

Barker instead discovered the work of Patrick Merton and Bert Morton on transcranial electrical stimulation.[8] It seemed that it was possible to stimulate electrical circuits in the

brain directly and produce effects without permanently affecting the memories and personality of a human volunteer. The problem was that the amount of electricity required to get through the bones of the skull was painful on the skin, and could lead to burns. In line with his original vision, Barker's new approach offered an ideal way around this problem, in that a magnet held near the scalp can induce changes in the electrical fields below – without having to travel through scalp or skull. There is no pain; there are no burns. Barker and his group tried it out and it worked. He organized to visit Merton and Morton in their department in London, bringing his home-made magnetic stimulator with him in two suitcases. They set their apparatus up in the laboratory in London and, holding a large magnetic coil over the vertex of the head, magnetically stimulated the brain of a volunteer whose hand moved without discomfort.

A series of phone calls brought others from elsewhere in London to the laboratory and transcranial magnetic stimulation (TMS) was born. Word spread quickly and Barker and his group did a number of public demonstrations of the new technique during 1985 at the Physiological Society meeting in Oxford and the 11th International Congress of EEG and Clinical Neurophysiology in London, at which they had queues of people lining up to be tested. They went back to base and constructed six machines of which one went to John Rothwell at the National Hospital for Neurology and Neurosurgery in Queen Square, one of the leading neurological centers in the world.

The first vision for TMS was that it would be used for diagnostic and research purposes. And it still has a place in these areas. Many departments of psychology and neurology have TMS machines to map brain functions. The technology allows researchers to pinpoint where in the brain certain functions are localized, or in some cases what areas of brain or peripheral nerves have been damaged in the case of brain disorders such as motor neurone disease or multiple sclerosis.

Barker formed a company with one of his PhD students Reza Jalinous[9] called Magstim based in Wales. This was one of four companies that began to supply devices for the field. The others were Cadwell Laboratories in Washington State, Dantec, a division of the giant medical devices company Medtronic, based in Michigan, and Neotonus in Georgia. Demand burgeoned. By the year 2000 there were 3000 papers on the use of TMS with a new paper appearing at a rate of 1 per day.[10]

TMS in psychiatry

At no point did it cross Tony Barker's mind that TMS might offer a treatment for any psychiatric disorder. The idea that TMS might have an application in psychiatry seems to have taken root simultaneously in several different settings in the early 1990s. The first published use came from Bonn in Germany, where Gerd Hoflich and colleagues tried TMS in two psychotically depressed patients who were resistant to antidepressants, prior to proceeding to ECT. Neither patient responded, although both later responded to ECT.[11] Another group in Krakow, linked to Jerzy Vetulani, also saw potential in the new method as a possible replacement for ECT – although no patients were reported.[12]

The first positive results came from Israel, where Robert Belmaker and colleagues at Ben Gurion University in Jerusalem began treating a series of patients, after first experimenting with TMS in an animal screening test for antidepressants – the Porsolt swim test.[13] This is a behavioral despair test, rather than a test that explicitly tries to model depression, but a number of antidepressants, and electroconvulsive stimulation (ECS) when given to animals, put off the onset of despair in this test. When TMS produced the same kind of results as antidepressants and ECS, Belmaker and others were interested. In 1994, he and his group reported the first beneficial effects of TMS in depressed patients at a European College of Neuropsychopharmacology meeting in Jerusalem.[14]

But the main action happened in the United States, in the NIMH/NIH, where almost unbeknownst to one another there were three sets of players, two of which were linked to Bob Post, who had a longstanding research program looking at the effect of anticonvulsants on mood, and another group that no-one was aware of.

In 1980, when reporting beneficial effects of carbamazepine for mania, Post had put forward a possible theoretical model as to why anticonvulsants might be what later came to be called mood-stabilizers.[15] He suggested that recurrent mood disorders and recurrent convulsive disorders might share a common pathophysiology according to which each convulsive or dysthymic episode kindled the next episode. This pointed toward the need for good anticonvulsant control in the case of patients with epilepsy and equally good anti-kindling control in the case of people with mood disorders, and perhaps this is what anti-convulsants in fact did.

This hypothesis was hugely influential during the late 80s and early 90s, particularly following the marketing of semi sodium valproate by Abbott Pharmaceuticals in the United States for bipolar disorder. It became common practice to review all anticonvulsants for possible mood stabilizing properties and for treating mania in bipolar disorder. Yet vigabatrin and topiramate appear not to be mood stabilizers and come at a very high cost in terms of side-effects; as well, other anticonvulsants such as lamotrigine may have antidepressant properties but do not have convincing mood stabilization properties. Nonetheless, there has been little serious questioning of Post's idea. The logical extension of Post's argument is to pick up patients who are thought to be prone to bipolar disorders early in life before their first episode and to start them on anticonvulsants from pre-school or certainly pre-teen years. This now happens widely in America – but not in Europe - suggesting that there was something peculiarly relevant to America in Post's original vision.

Whatever ECT did to get patients well, paradoxically almost, just like the anticonvulsants, it also raised seizure thresholds.[16] Post himself was not a fan of ECT but it made sense to see if this new possibly ECT-like technology, TMS, might also make further seizures less likely. He had a post-doctoral student working with him, Susan Weiss, whom he set to looking at this issue after the first reports of TMS's beneficial effects began to emerge. The Post team were interested in how one convulsion kindles the next. If the same thing happened in mood disorders, then what was needed was a

treatment that "quenched" the propensity to seizures. Weiss had developed an animal model of quenching and, working with this model, Weiss seemed to find that TMS quenched the propensity to seizures. This indicated reason to believe that TMS might be a beneficial treatment for mood disorders.[17] There was initial excitement but efforts to replicate this effect failed. Meanwhile, other developments were about to steer TMS in a different direction.

Visualizing the brain

The person whose work ultimately had the most enduring effect on how TMS is seen within psychiatry was Mark George. Having studied medicine at the University of South Carolina and then secured a place at NIH, George took a year out beginning in the summer of 1990 to do a fellowship at Queen Square Hospital in London with Mike Trimble, the doyen of British neuropsychiatry. Convinced most psychosyndromes would turn out to be brain circuit disorders, George was intent on training in both neurology and psychiatry. His conceptual approach to TMS was the one that captured the field in the mid to late 1990s. Trimble's team was based on the eighth floor, one floor beneath the lab of David Marsden, one of the leading authorities on movement disorders. One day while taking the elevator down, George met a man who was clearly puzzled and who explained his puzzlement – some doctors up there put a magnet on my head and caused my hand to move. George was so surprised by the account, or perhaps by the evident surprise that the man himself had displayed, that he immediately took the elevator back to the 9th floor to see what was happening. There he found one of the first groups to actively pursue TMS, led by John Rothwell. These investigators were using magnets placed over the top and middle of the head of subjects – the site of the motor cortex - to cause hands, arms or legs to move.[18]

Intrigued, George asked them whether they had ever considered moving the magnetic coil over the prefrontal lobes of the brain. They were surprised that anyone might want to do that. Neurologically, the prefrontal areas of the brain are largely silent. Nothing moves on stimulation, not fingers, arms, legs or toes, and if something doesn't visibly respond for most neurologists it doesn't exist.

But George's early work had been on neuro-imaging, which was just then coming onstream. PET scans and MRI scans were visualizing brains never visualized before and pointing to underactive and overactive brain circuits in conditions from Parkinson's disease to obsessive-compulsive disorder (OCD). One of the images that came into focus was that of the depressed brain, where it seemed there was reduced activity in the pre-frontal lobes.[19] This pointed to a pathology in the frontal lobes, or in the basal structures of the brain interconnected with the prefrontal lobes. If some treatment could be found that stimulated activity, any activity, in these areas, it might turn out to be a treatment for depression. Perhaps this was why ECT worked - the current in bilateral ECT is after all directed through the pre-frontal lobes.

George had to wait until he got back to NIMH to try out his ideas. He was scheduled to work in Post's group, but George had little in common with most researchers in the group

who were interested in neurotransmitters – for him the neurotransmitter paradigm, which viewed the brain almost as a chemical soup, made little sense. In contrast, the motor group in the neurological service at NIMH led by Mark Hallett had one of the few other TMS facilities outside of Queen Square, and Hallett and Eric Wassermann were using TMS in much the same way that it was being used in Queen Square. Nominally supervised by Post, George approached Hallett and Wassermann armed with brain scans showing prefrontal underactivity in depression. Hallet and Wassermann listened with interest but their reaction, like that of Post in psychiatry, was that this was an interesting hypothesis rather than systematic science. George was given the opportunity to use the laboratories early in the morning or late in the evening, when he wouldn't interfere with the real work going on. So all of the early work was done before 8 am, and after 7 pm.

George ran into problems and delays. Early work on TMS in neurological subjects had shown that it could occasionally induce fits.[20] Institutional review boards and ethics committees in the NIMH therefore wanted studies of healthy volunteers to establish the safety of the parameters being proposed for his work. No one knew what the effects of pre-frontal stimulation might be. No one knew either whether to stimulate the right or the left prefrontal region, or whether it was better to stimulate with a high or a low frequency. George undertook healthy volunteer studies to work this out.[21] He found to his surprise that left-sided stimulation seemed if anything to enhance functioning in healthy volunteers, where high frequency right-sided stimulation induced anxiety. In contrast, one person had a noticeable mood change after medial prefrontal stimulation – but he became sad and remembered a funeral scene. This individual also had a kick in his prolactin levels suggesting that the treatment was having an effect on deeper brain structures and might be close to causing a seizure. In general it appeared that TMS could also change peripheral thyroid hormone levels.[22] This was important in the longer run as it suggested that while the direct effects of TMS are on superficial areas of the motor cortex, these effects can trigger changes deeper in the brain.

It was clear that as part of the development of the new treatment, randomized controlled trials would be needed in which active TMS was compared with a placebo. George and colleagues devised a sham procedure. Active treatment would involve the traditional placement of the magnet in a position parallel to the head so that the magnetic field affected underlying electrical flows in the brain, while sham TMS used just the same magnets held in a position perpendicular to the brain so that there would be little effect on the underlying brain circuits. This was quite convincing in that one of the most salient aspects of treatment is the noise the magnets make and this was the same for both treatments.

George and colleagues then did a within-week crossover study on chronically depressed inpatients who were given sham TMS, or TMS over the left prefrontal lobes at 1 Hz or at 20 Hz or over the right prefrontal lobes at 1 or 20 Hz. They still had no idea whether to stimulate with high or low frequency, or over the right or left prefrontal cortex. In this single-blind randomized crossover study, active TMS produced no benefits over sham treatment – although it should be noted that convincing effects within a week have not

been found with any treatment for depression, except perhaps ECT. Again, they found that patients got more anxious with right stimulation, especially high frequency.

Combined, these results suggested that the best bet for treatment was repetitive high frequency left-sided stimulation of the prefrontal lobes. A new treatment, rTMS (repetitive TMS), was born. Whereas other investigators in the field were holding the magnetic paddles over the vertex of the head, just as the neurologists had been doing, or over the midline of the frontal lobes, George and his group were stimulating to the side and the front of the brain, driven by brain imagery of where the problem might lie. At the same time, George and Eric Wassermann had begun studies in patients who had OCD, and this gives the key to the thinking. In OCD at this stage, brain imaging studies seemed to show clear hyperactivity in what appeared to be a discrete brain circuit. Attempting to treat OCD with TMS was driven by a vision of neuro-circuits and the potential to interfere specifically with circuits that were visibly abnormal on brain scans, rather than to shake up the brain in general. Part of the problem in treating depression was that while underactivity of the frontal lobes had been described in a number of studies, the changes were much less clearcut than the changes reported in OCD.

In addition to the theoretical issues about where to stimulate, there were practical issues to consider also. George at this point was using a Cadwell machine. This had a tendency to "blow up" at six-monthly intervals, which meant the team had to have several machines. Also, the Cadwell was cooled by water, and in earlier models the water was only separated from a considerable electrical charge by a thin rubber ring. As a physicist put it to him at one meeting – he was going to die if he kept on doing TMS with this machine. (Similar exchanges in all probability played a part in the early history of ECT also.) NIH absolutely refused to support another of his proposals, which was to deliver TMS within an MRI scanner. Who knew what would happen if a powerful magnetic flux were created within a static magnetic field; the radiology department feared for the safety of the very building.[23]

In depression, they began with an open study. And in this there appeared to be responders. One was a woman from Maine who was a software developer and a pilot, with a ten-year history of treatment-resistant depression. She had previously responded to ECT, and to carbamazepine, but her responses had been transient. On the second week of rTMS, she showed a clear lightening of mood, which elated the research team. While treating her and others with rTMS, they also ran PET studies to see whether they could demonstrate actual brain changes at the same time that might coincide with any therapeutic response. This again brings home the difference of vision between what George was doing and what anyone else was doing at the time – this was the first report of brain imaging of TMS in depression.

For their first real treatment study, George had to justify to the NIH institutional review board his idea of pitting this new treatment against a sham treatment that clearly would have no effect. There was pressure on them to keep the sham treatment period short and so they opted for a two-week treatment period, reasoning that this was the minimum needed to see effects with ECT. There seemed to be benefits to rTMS but these were not

dramatic – but after all showing anything after two weeks was more than most people might have expected and these slender benefits provided real grounds for optimism.[24]

But by the end of 1996, George, Post, Belmaker and others were all to some extent trumped. Within NIH another research effort centered on TMS had taken shape. Alvaro Pascual-Leone was working at NIH on TMS with Hallett and Wassermann, at the same time as George. His research took a standard neurological approach to TMS but he became aware of the work of George, Belmaker and others within psychiatry. Pascual-Leone returned to Spain and in very short order recruited a group of psychotically depressed subjects to a study in which high frequency left prefrontal rTMS was compared to sham TMS. The results reported in the *Lancet* showed that in 17 patients with medication-resistant psychotic depression, the severest kind of depression, there were dramatic responses after a week of treatment. "Our findings emphasize the role of the left dorsolateral prefrontal cortex in depression and suggest that rTMS of the left dorsolateral prefrontal cortex might become a safe, non-convulsive alternative to electroconvulsive treatment in depression."[25]

George, Belmaker and others were stunned. Someone working in their midst had managed to pull off a study like this without any of them aware that it was being undertaken. The outside world was electrified. There was intense interest in the new treatment. Within three or four years most departments of psychiatry in Germany for instance, a country that had traditionally been hostile to ECT, were engaged in TMS research. When a Chair in psychiatry in Berne fell vacant, half the applicants listed TMS as their research area of interest. A swathe of countries from Holland, Belgium and Germany through to Japan, in which ECT was banned or restricted, saw an upsurge of interest in TMS. In these countries, which were often heavily orientated towards either psychotherapy or psychopharmacology, and in which the traditional physical treatments in psychiatry were often linked to the horrors of the Second World War, physical treatments once more appeared to offer possibilities.

If triggering activity in the frontal lobes of the brain mediated the therapeutic effect of ECT, it seemed reasonable that a method to induce focal changes in the brain, such as TMS, might do so much more selectively and might do so without producing the problematic side effects of ECT. All of a sudden the arena of physical treatments was transformed from one where, it seemed, all the key theoretical breakthroughs had been made 40 years beforehand -- and the only thing that remained to be done was to modify the machinery --, into an arena in which it seemed possible to develop new treatments that might avoid the seizures and stigma of ECT and in which research seemed driven by theoretical questions that excited many psychiatrists and neuroscientists in a way that psychopharmacology had long since failed to do.

In many respects, TMS looked much better than ECT in that the obstacles to effective ECT treatment didn't apply to TMS. In the case of ECT, the bones of the skull and the oiliness of the skin and a person's hair all got in the way of the effective transmission of an electrical signal. It was impossible to judge just how much electricity was needed to trigger a seizure other than on a trial and error basis and by using rules of thumb such as

the rule that older people in general needed a higher dose than younger people as the skull thickens with age. But even within the skull itself there are fissures where the bones of the skull connect and these provide sinks through which electricity can pass particularly quickly. The siting of these fissures will vary from person to person and for this reason some individuals may get a quite different distribution of electricity within their skulls than others. With TMS on the other hand the skull was transparent. The reversing magnetic fields alter the current in the brain cells underneath it without anything having to travel through the skull.

The big drawback to TMS however was that it did not penetrate the brain to any great depth. If the effects of ECT are mediated through some action of the seizures or the electrical current on deeper brain structures such as the thalamus, hippocampus or other structures within the neuroendocrine system, then TMS was at a competitive disadvantage. There would then only be two ways to compete with ECT. One was by changing cortical circuits that in turn modified deeper circuits, but in the late 1990s this remained at the level of aspiration. The only possibility was to reach deeper into the brain by using TMS to produce a seizure. It was this latter possibility that led Harold Sackeim in the first instance, allied with Holly Lisanby at Colombia, and Thomas Schlaepfer in Berne to take the opposite approach to Mark George: instead of avoiding rTMS-induced seizures, they would crank up the intensity of the stimulation in order to trigger seizures.

Left or right?

TMS came with a natural ally, in that its development coincided with the development of brain imaging techniques and their diffusion. Researchers could look at what was happening in the brains of patients being given TMS. Did the reduced blood flow or hypofrontality found in depression reverse itself with ECT or TMS? Did left-sided TMS produce benefits where right-sided TMS didn't? These were ideas that George helped kick off, but the questions had been raised even earlier in the work of Harold Sackeim.

Sackeim had trained in psychology in Philadelphia before moving to Columbia in 1977, where he ended up in a post split between Columbia and New York University's new clinical psychology training program. One of his main interests was in the neuropsychology of affect and in particular the lateralization of affect. The Psychiatric Institute at Columbia exposed him to ECT, and he realized this offered a wonderful opportunity for research on emotions and their possible lateralization in the brain. In 1980, he co-wrote a grant application with Sidney Malitz to look at the affective and cognitive consequences of ECT. In the midst of an administrative crisis, PI turned to Malitz to be its director, and this left Sackeim holding a funded grant on ECT, never having even seen ECT at this point.[26]

Completely new to the field, Sackeim began asking a number of questions aimed at controlling the research done. What was the right dose? It turned out there was no consensus on this issue, partly because the seizure was seen as the mediator of benefits and the electrical current was viewed as almost incidental. This had been the central tenet

regarding ECT's mechanism of action, since it was put forward by Jan-Otto Ottosson in 1960. But for a study of the cognitive effects of ECT, some of which were thought to be linked to the electrical current, there was clearly a premium on controlling the dose of electricity. As part of their research Sackeim and colleagues devised a protocol that involved titrating the dose of ECT so that patients had a sufficient dose to have a seizure but not so high a dose that surplus electricity might cause cognitive problems.

One of the other methods to manage the cognitive problems of ECT was to use right unilateral rather than bilateral ECT. The rationale here was that as the right hemisphere of the brain is the non-dominant one, passing the electricity through this hemisphere would lead to a generalized convulsion, but in a manner that would localize the electrically induced side-effects to the right hemisphere only. As this was the non-verbal hemisphere of the brain, the hope was that verbal or memory related material would be spared. A series of research programs starting with Richard Abrams in the 1970s had suggested that this might be the case, but successive projects and later clinical practice indicated that patients treated with right unilateral ECT were less likely to recover or were slower to respond to treatment. This was puzzling in that a form of treatment that produced seizures didn't seem to produce recoveries. This was very clear in the case of patients entering Sackeim's research, where right unilateral treatment was given at a much lower dose than previously. The differences between bilateral and unilateral treatments were stark.

One interpretation of this finding was that the point in the brain through which the current passed was critically important to the therapeutic response. If this was the case, the possibility opened up that benefits might be produced by electrical currents without inducing seizures. An alternative was that far from the effects of ECT being mediated through some generalized consequence of a seizure, such as a neuroendocrine effect, there was something more localized or focal about the effect of a seizure that mediated the therapeutic effects.

As it transpired, benefiting from his position in PI, Sackeim's group were among the first to produce brain images of altered frontal lobe functioning in depression. Imaging the brain after effective bilateral ECT showed a shut-down of function in the frontal lobes, which Sackeim interpreted as an inhibition, whereas unilateral ECT showed inhibition of the motor strip only but not the frontal lobes.[27] These findings suggested that one reason for the failure of right unilateral ECT to produce the benefits of bilateral ECT was that right unilateral stimulation failed to trigger a seizure in the frontal lobes to the same extent as bilateral, and failed to induce a post-ictal inhibition of some key activity. If this were the case, one possibility was to increase the dose of the stimulating current used in unilateral therapy. A higher dose would ensure current got into the right frontal lobe and a seizure was triggered there.

At this point Sackeim's work began to converge with the emerging field of TMS, and specifically with the work of Mark George. This was reflected in a editorial debate between George and Sackeim in 1994 in *Convulsive Therapy*, where George proposed that subconvulsive brain stimulation might produce a cure in depression, while Sackeim

argued that the new field of magnetic stimulation might be better off aiming to trigger seizures rather than trying to avoid them. This was a first proposal of the idea of magnetic seizure therapy.[28] At this point, Sackeim was joined by Holly Lisanby from Duke University and her brief within the group was to help develop MST. This first required a grounding in the new field of TMS.

George's contribution offered a first clear articulation of the idea that a seizure might not be necessary for ECT,[29] a heretical idea for some, and simply not worth taking seriously for others. The battle lines were most clearly drawn between George and Max Fink. Sackeim was initially in the middle, but the developing logic of the Sackeim position drew him closer to George.

The next step for Sackeim was to see what happened with right unilateral treatment delivered at a higher dose. In a series of studies Sackeim suggested that right unilateral ECT at higher doses produced comparable benefits to bilateral ECT while at the same time sparing cognitive capacities. Fink and Abrams responded that right unilateral ECT, no matter how high the dose, remained less effective than bilateral ECT and that at higher doses the adverse cognitive effects of right unilateral ECT were as obvious as any following bilateral ECT.

The issues developed a generational flavor. On the one side was an old guard denying there was any problem with the standard treatment. On the other was a group of younger researchers armed with a battery of new technologies. The ability to visualize the brain almost forced new questions, and certainly threw up new grant getting opportunities. A series of new therapies also began to hover on the horizon – vagus nerve stimulation and deep brain stimulation. Money and influence began to drift toward the younger generation. The journals, and organizations within the field demonstrate the shift well.

In 1947, a new Society of Biological Psychiatry (SBP) began, with a new journal *Biological Psychiatry*, just the same time as an Electroshock Research Association (ESRA) was developed by David Impastato, William Holt, and Zigmond Lebensohn. ESRA published its proceedings in a Swiss journal *Confinia Neurologica*. In the late 1950s, a carbon dioxide therapy association formed around Meduna, and this group published their proceedings in yet another new journal - *Journal of Neuropsychiatry*. By 1960, the three societies recognized that they had similar interests, and SBP absorbed the other two in 1963. But the resulting society was plagued by a dynamic that has been common to psychiatric and psychopharmacological societies ever since – it became polarized between a group of clinicians who saw themselves as trying to advance therapy (those who had formerly been in ESRA and the Carbon Dioxide Association), while the SBP wing saw themselves as "scientists."[30] With the decline of ECT in the 1960s, the SBP wing won out.

When the California legislature passed anti-ECT legislation in 1974, Gary Aden of San Diego organized a ginger group to oppose these developments. (see chapter 10) This first met in May 1975 in conjunction with the annual APA meeting. In May 1976, this became the International Association for the Advancement of Electrotherapy (IPAAE).

At first, IPAAE was largely a "political" organization composed exclusively of clinicians, but in the late 1970s, they began inviting attendees from the main APA meetings, such as Max Fink and Dick Abrams, to contribute. By 1984, IPAAE meetings were organized around invited speakers on ECT topics.

In 1984, Fink established a new journal *Convulsive Therapy*, which had its first issue in early 1985. Looking for a membership organization that would support the journal, he turned to IPAAE, who made CT its official journal in 1986. IPAAE then changed its name to the Association for Convulsive Therapy (ACT) and membership included a subscription to CT, of which Fink was editor from 1985 to 1994, when Charles Kellner took over, who in turn was succeeded by Vaughn McCall in 2004.

In 1997, a number of new members were suggested for the editorial board of CT, who were distinguished by their interest in TMS rather than in ECT. By 1999, these new board members pushed through a change in the name of the journal to *J ECT*: Dedicated to the science of electroconvulsive therapy and related treatments. This continues to be the name even though very few papers on TMS have actually appeared in *J ECT*.

By 1999, TMS featured prominently in symposia at ACT's annual meeting, and since then Vagus Nerve Stimulation (VNS), and more recently MST have featured. Meanwhile, the APA Task Force on ECT, also had a name change to Corresponding Committee on ECT and other Electromagnetic Therapies, and, as of 2004, the Task Force has been chaired by Holly Lisanby, whose primary background was not in ECT.

The split between the new and the old guard was portrayed by Sackeim in 2004 in a pair of editorials written for *J ECT*, in which he viewed himself and other like-minded researchers as occupying a middle ground, under assault from the Church of Scientology on the left and from the old guard in ECT on the right. The old guard according to Sackeim believed that ECT properly used was almost universally effective and never caused problems, and this obviated the need for any further research.[31]

In contrast, rTMS for instance appeared as rational a treatment as could be wished for. George had linked TMS usage clearly to an effort to alter blood flow through the prefrontal cortex in a manner that would reverse the established problems in this area. Not only this but increasing the TMS dose appeared to have a bigger effect on changes in blood flow, opening up the possibility of making this form of treatment very rational and predictable. Investigators subsequently looking at effects on the biochemistry of the brain, such as alterations in neurotransmitters like dopamine or in terms of immediate early genes, found that TMS produces effects that mapped onto those previously reported for antidepressants.

When in doubt electrify - the lure of electromagnetism

But all was not as it seemed. The first problem was that Pascual-Leone's research that had done so much to electrify the field turned out to be mysteriously unreplicable. No one else has been able to show a comparable response in psychotic depression, and no

one has been able to show any clear response in any kind of depression within a week. When researchers from Germany, through to Japan, and from Brazil to Canada began to get into the business, a host of trials were launched many of which were negative.

The negative findings could be explained to some extent on the basis that trial protocols were still limited to two-week studies for the most part, and by the fact that the dose of treatment, and the best site for stimulation had still not been worked out. There were even doubts as to the best shape of the coil - a variety of coil shapes were possible, each of which might have delivered different results, but these hadn't been systematically tried. Combined with different intensities of stimulation these might produce a broader effect on the brain with greater biological consequences.

However, from within the field Thomas Schlaepfer and others meta-analysed the published studies as of 2003 -- limited to those studies with reasonable protocols and where results were adequately reported -- and came to the conclusion that "current trials are of low quality and provide insufficient evidence to support the use of rTMS in the treatment of depression."[32] The treatment appeared to have some effect on mood, but not a sufficient effect that it might replace anything in the therapeutic armamentarium in the short run, and definitely not ECT. Some within the field all but accused Schlaepfer of attempting to sabotage developments, but in one sense, this simply restored rTMS to the researchers. It was a tool that produced clear changes in brain function, that could be used to map out further interactions between brain circuits, and one that held some promise in that there appeared to be a distinct if somewhat minor effect on mood. This reasonable position, which was the George position prior to the fuss generated by Pascual-Leone, was however not the kind of message the field was looking for and the bubble that had surrounded rTMS began to deflate.

The Pascual-Leone episode, however, was not an aberration within an otherwise rationally developing field. Within the new guard the competition was intense, different parties jockeying for priority on treatments from TMS through MST and on to vagus nerve stimulation and DBS. At one point, one of the early movers in the field, about to deliver an invited lecture, found himself faced with a statement to sign renouncing priority in the development of one of the new treatments that might have interfered with the patent application of his host – failure to sign and the lecture would be cancelled.

But there was another electrical wraith hovering in the scientific machinery. When Belmaker, George, Post, Lisanby, Weiss and Pascual-Leone met in December, 1996, at Puerto Rico,[33] the first question for the workshop was what are the differences and similarities between electrical and magnetic stimulation of the scalp particularly on the depth and magnitude of neuronal excitement? None of the participants appeared to be aware of the prior existence of transcranial electrical stimulation, or of the history of electrotherapeutics dating back 100 years or more. The notion that they might be reinventing the wheel was not welcomed and didn't lead to any obvious skepticism regarding what they might be seeing.

Efforts to get to grips with the history of ECT hitherto have often subsumed it into the history of medical electricity. The opening chapter of Timothy Kneeland and Carol Warren's *Pushbutton Psychiatry* details the origins of medical and therapeutic interest in electricity in Hippocratic medicine.[34] Part of our fascination with amber supposedly comes from a recognition by the ancients that amber could be electrified by friction, and the term electricity itself comes from electron, the Greek word for amber. The present history sees ECT in terms of the convulsion produced, rather than as another episode in the history of medical electricity. Electricity is incidental to the story of ECT as told here, but the history of medical electricity is highly germane to the TMS story.

Just as Tony Barker initiated the history of TMS by using magnets to trigger selective movements in the digits of the hand, so also the discovery of animal electricity by Luigi Galvani involved demonstrations that the limbs of even inanimate animals could be made to move by the application of an electric charge to nerve endings.[35] This gave rise to a bitter dispute between Galvani, who proposed the existence of animal electricity, and Alessandro Volta who denied this possibility.[36] Galvani effectively won out within medicine, and efforts to follow his lead by seeing what happened when electrical charges were applied to the brain, in due course gave rise to a new therapy, Galvanism, and indeed pretty well to neurology as a discipline.

The outlines of Galvanism as a therapy had existed before Galvani. Earlier in the eighteenth century, John Wesley for instance had been using a machine to deliver electric shocks to his congregation. The first record of a patient with a clear mental disorder being treated with electric currents applied to the head stems from John Birch, a surgeon at St Thomas' Hospital, London, in November 1787. The patient, who had many of the classic features of melancholia, had his head covered with a flannel by Birch who "rubbed the electric sparks all over the cranium; he seemed to feel it disagreeable but said nothing. On the second visit, finding no inconvenience that ensued, I passed six small shocks through the brain in different directions. As soon as he got into an adjoining room, and saw his wife, he spoke to her and in the evening was cheerful, expressing himself as if he thought he should soon go to his work again."[37] When seen three months later this man apparently remained perfectly well.

Galvani's breakthrough lay in his recognition of what happened when electricity was applied directly to nerve endings. He saw electricity as the agent of nervous action. But stimulating nerve ends directly wasn't necessary for the new therapists, in that most people understood electricity to be in essence a fluid of some sort, like ether, whose application to any part of the body could have tonic effects.[38] The issue was much more a case of devising new methods to deliver this effect, and an industry developed to meet the new need.[39] By the early nineteenth century, the potentially invigorating effects of electricity had become sufficiently established to feature prominently in Mary Shelley's *Frankenstein*, whose creation was of course brought to life by electricity.

There was a steady pace of developments in the electrical field through the nineteenth century. In 1831 William Faraday discovered the interaction between electrical currents and magnetic fields and how to convert mechanical energy into electrical currents. James

Clarke Maxwell linked electricity and magnetism in one of the first great unifying theories of physics. In 1875 Alexander Graham Bell invented the telephone and in 1878 Joseph Swan developed the filament lamp. In the 1880s cities began to be lit up with electricity and tramways began service.

Against this background, electrotherapeutics flourished. French, German and English alienists published on the field. In 1855 Guillaume Duchenne wrote "A Treatise on Localised Electrization and its Application to Pathology and Therapeutics."[40] Emil Du Bois-Reymond had also published a treatise on "Investigations on Animal Electricity."[41] The study of Galvanism and electrotherapeutics began to pull the discipline of neurology into existence, and to establish a role for neurologists in the management of patients who would later be regarded as having psychosomatic problems.

In the 1870s, a series of British hospitals had set up electrical rooms in which electricity was used to treat patients. Very early on medical practitioners from the most prestigious hospitals began to complain about the use of electricity by quacks.[42] As might be expected, the medical view was that only those specialized in the use of electricity and capable of understanding clinical pictures should be permitted to use these methods for therapeutic purposes. Alan Beveridge has argued that there was a premium on the asylum doctors taking up the use of electricity, as the notion of physical treatments endorsed their claims that insanity was a medical disease appropriately treated by medical practitioners rather than by moral or other means in asylums or other institutions run by non medical personnel.[43]

The forms of treatment were continuous current treatment – Galvanism – or treatment with induced currents – Faradism. These were both extensions of the methods used by Wesley and others previously, which had involved the delivery of a shock by means of frictional or static electricity. An alternate approach had been to insulate the patient, electrify him and draw sparks from him.[44] The course of the new galvanic and faradic treatments ranged from a few days to several months, with therapy being applied in daily or alternate daily sessions, lasting for anything from 10 to 20 minutes. In the mid-nineteenth century, the electrodes were often placed on the patient's hands but as the century went on they migrated to the head. The patients treated in this way, especially within the asylums appear to have been predominantly depressive.[45] Occasionally, electrical treatments were linked with the induction of epileptic convulsions but convulsions were thought to be undesirable and in the main physicians preferred weaker currents to strong ones.[46]

Toward the end of the nineteenth century, however, electricity began to fall out of favor in the asylums. Even though dramatic responses had been reported in patients who had been insane for seven years or more, in general within the asylum the treatment didn't have the same degree of success that physicians treating patients with nervous complaints rather than insanity were reporting. Among those treating psychosomatic patients with electricity were some of the most famous names of the day such as George Miller Beard, who described a new syndrome neurasthenia that might have been conjured into existence for the purpose of response to electrotherapy.[47]

A range of theories developed to supplant the early theory that electricity provided a fluid that entered the body and exercised a tonic effect. Some thought electricity was stimulating, while others believed it sedative.[48] In a distinct echo of the TMS field, some thought it increased the blood flow to the brain[49], while others argued that it decreased blood flow.[50]

Poor results with electricity were put down to the fact that doctors or quacks had not followed guidelines, not understood the nature of electricity or had not chosen the correct patients. As Beard put it: "There is a vulgar error abroad, both in England and the United States, that any "Old Granny" can make applications of electricity …… No man can apply electricity with a higher success until the details of the application had become to him a matter of routine, so that he can use any one of the methods on any kind of patient without fear or doubt. Skill of this sort in any art, cometh not of observations, it is acquired only by careful, studious and repeated experience."[51]

But interest in electrotherapeutics began to wane at the turn of the century even in neurology. Commenting in 1901 on trends in the use of electricity, Lewis Jones noted that, "The employment of electricity in medicine has passed through many vicissitudes, being at one time recognized and employed at the hospitals, and again being neglected, and left for the most part in the hands of ignorant persons, who continue to perpetrate the grossest impositions in the name of electricity. As each fresh important discovery in electric science has been reached, men's minds have been turned anew to the subject, and interest in its therapeutic properties has been stimulated. Then after extravagant hopes and promises of cure, there have followed failures, which have thrown the employment of this agent into disrepute, to be again after time revived and brought into popular favor."[52]

As the neuroses became psychoneuroses, the possibility opened up that the effects of such an unquestionably physical therapy as electrotherapy might stem primarily from suggestion. A London physician, Hector A. Colwell, struck a more skeptical note in 1922: "On the occurrence of cases which refused to yield to any ordinary remedy, the mandate 'Let them be electrified' has often been issued, too frequently, rather with a vague hope of obtaining relief from an extraordinary remedy than from any well defined view of its real influence."[53] In this case, though, Colwell's skepticism was also a vivid demonstration of the ebb and flow of fashions in medicine, in that he was in fact citing the 1841 words of another physician, Golding Bird.

By 1922, electrotherapeutics was dead. But it came back in two forms. One was in the form of transcranial electrical stimulation (TES). TES was essentially a derivative of Galvanism, and goes back at least to Stéphane Armand Nicolas Leduc in 1902 and possibly before, depending on definition.[54] Merton and Morton were using TES as an investigative tool when Barker began his TMS experiments, but thought its use was limited by the pain it caused. For several decades previously however TES had flourished within the Soviet Union as a therapy, with clinicians claiming benefits in a range of psychoneurotic conditions. And there is unequivocal evidence that direct

transcranial electrical stimulation can modify most of the cortical circuits that TMS can modify[55], leading researchers in Boston and elsewhere to point out that TES might be equally effective as TMS but a much cheaper option than TMS for countries in the developing world[56].

The difficulty in distinguishing between fast and slow nerve fibres, that Barker had sought to solve by introducing TMS, in fact also produced another therapy that everyone concedes works – albeit with a modest effect – transcutaneous electrical nerve stimulation (TENS). The easiest nerve fibres to stimulate electrically are the slow fibres, and these can in turn block transmission through other pathways. This forms the basis for what is now known as the Gate-Control theory of pain put forward by Ronald Melzack and Pat Wall in the 1960s. In the 1970s, this phenomenon was utilized as a therapeutic procedure in chronic pain syndromes and in labor.[57] While TENS is now widely employed in hospital settings, there is also a flourishing undergrowth of companies offering variations on TENS, such as Alpha-Stim, which purport to be treatments for anxiety and depression. These firms offer FDA "registered" devices, that aim to restore harmony to the electrical balance of cells, organs and bodies.[58] While TENS unquestionably works, many of these related devices resemble the electrotherapeutic apparatus of a previous century and appear targeted at a psychosomatic marketplace.

The faithful assembled at the ACNP workshop in 1996 were largely ignorant of this backdrop. Given the dramatic findings of Pascual-Leone and the very visible changes in brain blood flow in response to rTMS, there seemed every reason for them to disregard history and continue to believe that what they were seeing represented a radical break with the past. Yet historical cycles have a way of reasserting themselves, and the results from blind trials suggest that a good deal of the TMS craze to date has represented a further chapter in the history of electrotherapeutics rather than anything else. There are in fact companies delivering rTMS therapies in Canada and elsewhere that seem indistinguishable from Alpha-Stim. These companies and their glossy brochures seem to be feeding from the same population as the patients visiting neurologists at the turn of the nineteenth century for the latest electrotherapy. This is a history in which small gains are being made, but which is open to gross exploitation, as the history of another electrotherapy – VNS – risks illustrating.

Vagus nerve stimulation

Interest had been growing in a possible relationship between anticonvulsants and mood stabilization. This began with the discovery of the possible mood enhancing or stabilizing properties of valpromide, a drug first used as an anticonvulsant in epileptic patients in Lyon in France in the mid-1960s. Important as well was the almost simultaneous discovery of the mood stabilizing properties of carbamazepine in Japan in the early 1970s. This interest was captured by Bob Post in his kindling hypothesis of mood-stabilization.

A mania for anticonvulsants developed, so that it was assumed almost any anticonvulsant would be a mood stabilizer. This led for instance to an explosion in the use of gabapentin

(Neurontin) in the late 1990s, fuelled it appears by a series of ghost-written and other articles planted by company (Warner Lambert) personnel, or experts writing at the behest of the company, in a series of journals that suggested gabapentin would be effective for mood disorders.[59] At one point gabapentin was grossing $1.3 billion a year, a very large proportion of which came from its off-label use as a mood stabilizer. The bubble was punctured when a randomized controlled trial demonstrated that gabapentin had little if any mood stabilizing property.[60]

This background set the scene for the discovery or creation of another mood-stabilizer. In the late 1980s a new treatment was introduced for refractory epilepsy – vagus nerve stimulation. The vagus or tenth cranial nerve is unique, in that, linking heart, lungs and other major organs with the brain, it is composed primarily of fibers that run from these organs to the brain rather than, as in the case of the other cranial nerves, fibers running from the brain to innervate muscles or organs. This fact about the vagus was known from the 1930s.[61] And indeed there are good grounds to think the brain is more concerned about events happening inside the body that anything happening in the environment. A full bladder or bowel tends to grab our attention just as much as any threat in the environment does. We however tend to forget about what might be called the visceral brain and think only of auditory or visual brains.

An awareness that stimulating the vagus nerve could influence those brain areas receiving fibers from this nerve, and that stimulation delivered in this way might be anticonvulsant, developed in the mid-1980s through the work of Jake Zabara, an electrophysiologist at Temple University in Philadelphia.[62] Zabara found that vagal stimulation in dogs suppressed seizures. He trailed his idea around device companies but got nowhere until Reese Terry at Intermedics responded. But this was outside Intermedics' core area, which was cardiac rhythm management, and they stalled on the project. Terry remained enthusiastic however and set up his own company in Houston in 1987, Cyberonics, having obtained the rights to the idea from Zabara.

Kiffin Penry and Christine Dean in Salem, North Carolina, treated the first patient with VNS in 1988 as part of a pilot study with patients who had treatment-resistant partial seizures and who were not appropriate for surgery.[63] This work was done in conjunction with Cyberonics, which by this stage had developed a repetitive mechanical stimulator, effectively a modified cardiac pacemaker for further studies.[64] (The technique involves implanting a pulse generator about the size of a pocket watch in the left chest wall to deliver electrical signals to the left vagus nerve through an electrode wrapped about the vagus nerve in the neck.) Using the Cyberonics stimulator, two open trials and then two randomized trials were undertaken. In the randomized trials, patients were assigned for a 12-16 week period to either low or high stimulation conditions with the low stimulation intervention being regarded as a placebo. These patients had on average a more than 20-year history of seizures, and were taking at least two anticonvulsants. Overall, the high stimulation group showed a 24.5 percent reduction in seizure frequency compared with a 6.1 percent for the low stimulation group.[65]

These results are not dramatic. But interest in the treatment developed on the back of results from follow-up studies. Seizure frequency seemed to diminish to an even greater extent over the subsequent year. VNS turned out to be quite different from other anticonvulsant treatments. It is not an acute treatment for convulsions, whereas others are. But while early trials demonstrated some anticonvulsant effect, VNS showed a developing anticonvulsant effect over time.[66] On the basis of these findings, VNS devices were approved in 1997 by the US Food and Drug Administration (FDA) for the adjunctive treatment of resistant partial and complex seizures. As of 2004, approximately 20,000 people have had implants.

True to anticonvulsant form, researchers on epilepsy clamped onto mood. Among the first was Gerda Elger, a neurologist from Bonn married to a psychiatrist, who claimed that there were positive mood changes in patients undergoing VNS that couldn't simply be explained in terms of improvement in the patients' epilepsy.[67] This finding was quickly picked up by Mark George and research groups active in TMS, for whom VNS appeared to offer another non-seizure- based physical therapy, and in addition a possible new research tool.[68]

As George was later to show, the vagus nerve stimulates areas of the brain that can be termed the visceral brain and brings about changes in the orbital cortex and other limbic areas that are at least as great as the changes occurring elsewhere in the brain in response for instance to loud noises.

The first person explicitly given a VNS implant for a resistant mood disorder was put on treatment in July of 1998 at Mark George's unit in the Medical University of South Carolina.[69]

Cyberonics, in contrast to George, saw a much larger market - the market being chased by Alpha-Stim and others. Panels of consultants were invited to explore the possibility that VNS might have a role in anxiety disorders, depression, obesity, Alzheimer's disease and virtually every possible other complaint in psychiatry. Satellite symposia, journal supplements and glossy reprints of early articles were sponsored. Attractive company representatives enticed clinicians to the company stand to hear about the new breakthrough. Investigators brandished PET-scan evidence that VNS treatment affected the metabolism of limbic structures in the brain; neurochemical studies in both animals and humans were said to show VNS effects on concentrations of monoamine neurotransmitters within the central nervous system. Partisans conceded that controlled trials were still needed and that animal and other studies were also required to support the new treatment. Yet confident that the results would come out alright on the day, a range of senior figures who might otherwise be extolling the virtues of the latest psychopharmaceutical claimed that the use of VNS in selected patients with treatment-resistant affective disorders was already warranted.[70] Cyberonics were bringing all the pizzaz of a Lilly or a Pfizer to this previously staid corner of the psychiatry world.

A first depression trial, the DO1 study, involved Lauren Marangell at Baylor in Texas, Mark George at the Medical University of South Carolina, Harold Sackeim at New York

State Psychiatric Institute and John Rush at the University of Texas at Southwestern. Thirty patients were recruited in the first instance and then a further 30 patients. The patients were a strange group with an average of 10 years' depression before they entered the study, a very high depression score on the Hamilton Rating Scale and on average a failure to respond to 16 distinct prior psychiatric interventions, including in two-thirds of the patients prior ECT.

Approximately one-third of the patients in this open trial showed some benefit, yet only 15 percent could be considered responders.[71] But just as in the epilepsy studies beforehand, whereas only 30 percent of the original group showed some response, this increased to 45 percent over the course of the year.[72] Furthermore, the best predictor of a failure to respond to VNS was prior treatment resistance – the most treatment-resistant patients proved treatment-resistant to VNS also. This opened to the door to considering what effect VNS might have in a less severely disturbed group.

A second trial, the DO2 study, was planned as a controlled trial, designed to get FDA approval for the treatment of depression. Even though the group were much less severely ill, it turned out the response rate to VNS remained at 15 percent while patients on sham VNS showed a 10 percent response. There was no statistical difference between the two groups. After 10 weeks of sham treatment, patients in that arm of the trial were switched to active treatment, and as in the previous trial, a year later up to 30 percent of patients were showing benefit.[73] The results however remained unpublished.

Another open study, DO3, was undertaken. In this the results were mixed, with a somewhat better profile in Europe than in the United States.[74]

Despite these relatively poor findings, VNS was approved for the treatment of depression in Europe. This occurred because medical device registration in Europe simply required a manufacturer to demonstrate safety. New devices did not have to be shown to work. Based on this VNS was licensed for use in Europe in 2003. The initial argument put forward for registration in the United States was that this treatment was registered in Europe, and it would seem anomalous not to have it registered in the United States as well. The company pushed for an expedited review and at an FDA advisory panel on June 15 2004, in a split vote the panel recommended approval for marketing. Cyberonics' stock jumped[75]. On August 12, however, FDA made it clear that the trial results were unconvincing and they did not intend to follow the panel's recommendation. Cyberonics' stock fell.At the start of February 2005, FDA re-opened the possibility of a future approval for VNS. Cyberonics' stock zoomed 30 percent.[76] Finally on July 15th 2005 FDA approved VNS for treatment resistant depression, despite considerable misgivings on the part of some of the approval panelists that it had in fact been shown to produce clinical benefits.

Cyberonics will almost certainly bring a commercialism previously found only in psychopharmacology into the heart of the physical treatment of psychiatric disorders. The pitch to the press by the company was that there were up to 4 million Americans with treatment resistant – or hard to treat depression – who might be candidates for VNS –

well over 1% of the population[77]. This was a much greater market than the market for VNS in epilepsy. As of the time of writing American psychiatrists are being flooded with brochures for VNS. Only time will tell what the cost of treatment will be with this device, which once inserted cannot ever be fully removed.

In epilepsy meanwhile, as of 2005, and a decade of VNS treatment, the therapy was linked to a number of fatalities – which FDA passed off as not yet replicated in the case of depression treatment. More to the point, the notion of mood stabilization, the idea that anticonvulsant treatments might help mood disorders by quenching kindling, just as they supposedly did for convulsive disorders, was looking shakier. In June 2005, an over 1800 patient controlled trial in epilepsy had shown there was little reason to think anticonvulsants quenched the risk of further fits in epilepsy. Patients who were not given anticonvulsants immediately after their first convulsion were at least as likely to be fit free as those given immediate treatment and those in whom treatment had been delayed or forestalled had a better quality of life than those who had been given immediate treatment[78]. Whatever about the complications of VNS, another treatment with an even greater potential for disaster emerged on the scene in the late 1990s.

Deep brain stimulation

From the 1940s, there had been evidence that cutting pathways in the globus pallidus or the thalamus could in some cases relieve severe tremor and other treatment-resistant aspects of Parkinson's disease,[79] and could also be beneficial in chronic pain syndromes.[80] The development of neurosurgery for Parkinson's disease ran in parallel with the development of psychosurgery for psychiatric disorders during the 1950s. When psychosurgery came under a cloud in the late-1950s, neurosurgery continued, although the focus of treatment in Parkinson's disease switched to the new pharmacological possibilities following the discovery that these patients showed a depletion of dopamine in their subcortical nuclei. This led to breakthrough treatments such as l-dopa. But the new pharmacological treatments aimed at replacing dopamine or stimulating the dopamine system. While producing miraculous cures in some, this did not put things right for everyone and a small number of patients continued to be candidates for surgery.

While surgery for Parkinson's disease would be an infrequent option, the need to intervene in chronic pain syndromes remained, as there were no comparable developments in the pharmacological management of pain. From the 1950s there had been reports of brain stimulation as a means to manage pain.[81] Then, based in part on the success of TENS, in the 1970s a surge of interest occurred in brain stimulation techniques as an alternative to surgery, and Deep Brain Stimulation (DBS) emerged.[82] These developments were encouraged by the discovery of endogenous opiate pathways in the brain.

Then in the 1980s, stimulated by developments in pain management, neurosurgeons interested in Parkinson's disease began to experiment with DBS as an alternative to the irreversible effects of surgical interventions in this patient group. The method aimed to knock out brain circuits by stimulation from implanted electrodes, which meant the stimulation could be turned on and off in order to track the effects of treatment. The

benefits seemed dramatic in many cases, and the treatment was publicized with videos of patients once unable to budge now able to move fluently about; moreover, their requirements for medication were dramatically slashed.

As with TMS, DBS depends on neuro-imaging technology. In order to implant the electrodes in the correct spot, it's necessary to be able to map the brain in great detail using both MRI and CT scans, fusing these with computer programs to get as precise a fix on the path of nerve tracts and blood vessels as possible. The consequences of a misplaced electrode can be hemorrhage and death. The 2004 remake of "The Manchurian Candidate" gives a reasonably accurate image of what the procedure looks like. When the electrodes are in place, the stimulation can theoretically work by either over-stimulating nerve cells, leading to somatic fatigue, or jamming the nerve cells, in either case producing a functional lesion.

Awareness of possible use of this technique in psychiatry grew following observations in Parkinson's disease that some electrode placements could trigger dysphoria – raising the possibility that the surgeons had tapped into a depression center.[83] These observations were reported widely in both the academic and lay media as dramatic new developments. As interest rose in the possible use of DBS in psychiatry, several groups had already made progress and one group in Belgium had just reported on DBS as a treatment for OCD.[84] As with reports in the field of electrotherapeutics from the late nineteenth century onwards, most of the key reports appeared in the *Lancet*.

OCD was the most likely candidate for the first studies of DBS. When the more general use of psychosurgery fell into disfavor, a number of centers in Sweden, Britain and elsewhere continued to undertake operations for refractory cases of OCD. This had always seemed to be one of the conditions that responded best to surgical approaches. Also, unlike depression, OCD was less of a reactive condition: the death of a spouse would not trigger a dramatic improvement in treatment-refractory OCD. OCD was one of the most sharply defined syndromes, and the arrival of brain imaging in psychiatry in the 1980s threw up clear-cut and discrete findings for OCD of increased glucose metabolism or blood flow in the medial and orbital frontal cortex and anterior cingulate gyrus, as well as in the caudate nucleus and the hypothalamus. Successful treatment, furthermore, whether with pharmacotherapy or behavior therapy, appeared to normalize these overactive circuits. It seemed that there was a clear target to aim at, and DBS promised to offer a way to test things out without producing irreversible changes.

Almost simultaneously, Bart Nuttin in Louvain in Belgium and George Curtis in Ann Arbor, Michigan, began to experiment with the possibility of DBS. Aware of emerging work in Parkinson's disease and pain syndromes, Nuttin spent some years sounding colleagues out about the possibility of DBS, aware that psychosurgery was viewed dimly and concerned that stimulation approaches, although reversible, might be viewed similarly. But the ethics committee at his hospital gave the go-ahead, as a few years later did an ethics committee in Paris, where psychosurgery was banned.[85] Many people it seems were happy to view this treatment in a very different light than psychosurgery, even though Nuttin and Curtis had to liaise closely with neurosurgeons in order to work

out appropriate sites for implants and were dependent on psycho- or neurosurgeons for the technical expertise to implant the stimulating electrodes.

Curtis's career is a microcosm of American psychiatry. Having graduated from Vanderbilt, he did a residency in McGill, where he engaged in research with Heinz Lehmann and Donald Hebb, and trained clinically with Bob Cleghorn at a time when Ewen Cameron was the department head. He undertook psychoanalytic training both in Montreal and later in Philadelphia. In Philadelphia, Curtis took up neuroendocrine research in the late 1960s at a time when stress hormones where coming into vogue and the dexamethasone suppression test (DST) was about to become a symbol of the new biological psychiatry. In the course of this research he heard a lecture by Isaac Marks on behavior therapy for phobias, and thought that exposure of phobics to threatening material would be a wonderful challenge to the endocrine system. Little came out of the biological research, which he undertook after moving to Ann Arbor, the home of the DST. Yet impressed by the response of phobic and, later, obsessive patients to exposure therapy, Curtis became a behavior therapist. This in due course left him with a cadre of therapy- and drug-resistant OCD patients; in 1995, looking round for something to benefit them and aware of the work on DBS for pain and tremor, Curtis wondered whether Deep Brain Stimulation might be the answer.[86]

The major firm in the field of making electrodes for the treatment of Parkinson's disease and pain syndromes was Medtronic, which provided electrodes for both Nuttin and Curtis, but which otherwise showed almost no interest in developing this new line of therapy. Curtis and his colleagues were held back by the fact that Ann Arbor was a small town and patient recruitment was painfully slow. But Nuttin was at a larger center in Louvain, and Medtronic's interest was stimulated in 1989, when Nuttin and colleagues reported benefits of deep brain stimulation in OCD.[87] A short while later Mallet and a group in Paris also reported that obsessive features appeared to improve in patients otherwise receiving DBS for Parkinson's disease.[88] The company convened a meeting of interested groups.

One of these was a collaborative group based in Brown University and the Cleveland Clinic, who had an active ongoing psychosurgery program for OCD. Among the key players here were Ben Greenberg, who had previously worked with Mark George and others at NIH on TMS, and Steve Rasmussen, who had previously been involved in establishing the credentials of selective psychosurgery for OCD.[89] This group, who had already been investigating the possible benefits of TMS for OCD, got involved in DBS and within a short time had developed the largest patient series.[90] By the time Curtis and his colleagues were able to present results from their small series of patients[91], they had all but been written out of the history.

But the Holy Grail for DBS is treatment-refractory depression rather than OCD. As of 2005, a number of groups are chasing success in this area. Unlike OCD, however, there is at present no consensus on what circuit is affected in depression, and without such consensus many question whether the hazards of treatment are worth it for a condition that, unlike psychotic depression, sometimes clears up miraculously on its own. DBS

may well offer benefits, but efforts to develop it, at least for depression, would seem to have the potential to inflict the kind of damage on psychiatry's current crop of physical therapies that psychosurgery inflicted in the 1950s.

The first claims of success came from a group based in Toronto and Emory. On March 1st 2005, the Toronto Globe and Mail told the story of Jeanne Harris, a former psychiatric nurse, who had sobbed through an entire summer, spent 6 months in bed, and shunned food and friends. She had been so depressed for 10 years, she was "willing to let doctors drill two holes in her head and implant electrodes in her brain, in one of the most radical mood-altering experiments on the medical books"… "It is an unbelievable, dramatic change for me", said the 50-year-old Mrs Harris. "For the first time in 10 years, I feel alive, I have energy, it's like a light bulb being turned on"[92]. In the uncontrolled study behind the headlines, 3 of 6 patients demonstrated an apparent response to DBS[93]. While many of these patients had had prior episodes of depression, and prior treatments, there was little about the patients' details that would have categorized this as a severely depressed group. Two had had to have the treatment withdrawn for complications. None of the six patients seemed to correspond to Jeanne Harris as portrayed in newspaper accounts of the research.

DBS was intriguingly portrayed in the Globe and Mail. "Unlike ECT, which shocks the entire brain with electricity to induce brain seizures … , DBS is designed to electrically stimulate only the brain region known to be overactive in people [who are depressed]… It is part of an expanding field known as brain pacemakers… DBS is less painful than ECT… However researchers could not first test their hunch in any animal model.. and there were risks: a small chance of brain hemorrhage or seizure. But when Ms Harris read through all the information, she didn't hesitate to sign up: 'It seemed to make sense to me. At that point, I didn't care. I didn't even care if it killed me' … For Ms Harris, who now shops, throws dinner parties and visits the library, the effects of the new implants were immediate: 'When I first came home, I was out with a hat covering the staples on my head and cutting back the hedges that had overgrown for so long … I felt that good'". Slipped into the midst of this account was a brief mention that even Jeanne Harris had had to have an adjustment to the stimulus frequency after several months in response to continuing bouts of depression – although these were reported as being briefer and milder.

The Toronto/Emory group were working with Advanced Neuromodulation Systems to push the new therapy forward[94]. And this alliance involved a novel development trajectory. The leads used were standard and easily reproduced, and brains are brains, but the new research team took out a patent on developing the stimulation of a particular brain area – area 25. This area identified from brain scan studies by Helen Mayberg, the lead investigator, was not widely accepted as the obvious target. But what to make of Mayberg's findings that patients with leads put in to this area, often reported an almost instant lifting of mood once the stimulation was turned on?

What might be going on and also the potential for damage with DBS can perhaps best be brought out by the fact that DBS is far from being a novel treatment in psychiatry. DBS

was first undertaken in Tulane University New Orleans in the early 1950s by Robert Heath[95]. This was before the era of chlorpromazine and the development of a neurotransmitter paradigm in psychiatry and Heath and colleagues were as focused on brain circuits as any modern researchers. In the course of this work, the Tulane group were the first to stumble on to the fact that the brain has pleasure centers and punishment centers. Depressed patients with electrodes inserted in the 1950s reported strikingly similar changes to those that seemed to Mayberg and colleagues to all but prove the validity of DBS.

While some of those within the field of DBS are aware of what happened at Tulane,t here is a more general amnesia surrounding the Tulane precedent that must stem in part from the fact that this research program later came to be seen as perhaps more problematic ethically than anything else in the domain of physical treatments in psychiatry. There were two problems in Tulane. First the fact that patients were operated on apparently for therapy, but in fact for research. And second, Heath and colleagues did not shrink from their discovery of pleasure and punishment centers but rather inflicted aversive stimulation on many subjects to explore the consequences and adopted these methods in an attempt to change behaviors such as homosexuality. This was close to the use of DBS to brainwash depicted in the remade Manchurian Candidate.

On the Brink of a New Era?

The sometimes not so civil war within the shock therapy field has perhaps in its own way delivered outcomes that neither side expected, but that both can celebrate. While none of the new therapies appears remotely as effective as ECT, in recent years the language of depression and indeed of psychiatry has been changing. Where once there was talk of serotonin levels, and such talk still dominates popular debate, in academic journals this language has been relegated to the level of advertising copy. The academic talk instead is of brain circuits and neural plasticity.

This change seems attributable to the efforts of both the seizure and anti-seizure camps. The work of George and Sackeim to visualize circuits played a part in this. In 2004 George finally got to report on the outcome of setting up a magnetic flux within an MRI scanner, the maneuver that NIH balked at doing out of concern for their building. This demonstrated that prefrontal TMS could in fact activate subcortical circuits, and it opens up new vistas for research of this type.[96] He was also able to activate VNS devices within the MRI scanner – turning on pacemakers in an MRI scanner is a complete contra-indication ordinarily for fear of what can go wrong for the patient. Again this demonstrated a first visualization of the functioning of what can be termed the visceral brain.[97]

These are substantial scientific developments, whether they have a therapeutic application or not. While clearly the work of George and Sackeim has played a part, research on seizures has had a key role in changing how mood disorders are "seen." In 2000, Tom Bolwig and colleagues were one of three groups to report that ECT produces neurogenesis in the hippocampus.[98] It had been thought for a century that nerve cells uniquely could neither replicate nor regenerate after birth. Bolwig's discovery has turned

this wisdom on its head, and has led to a scramble to see whether antidepressants and other therapies such as TMS might do something similar, with claims for success when these therapies give hints that they might reproduce some of the effects of ECT. Within a year reviews began to appear in major journals changing the language of depression and psychiatry from a language of neurochemical soups to a language of circuitry and neural plasticity. It seems clear that psychiatry – or at least its clinical neuroscience division -- is in the midst of a paradigm change.

Where Sackeim and George have focused on stimulating specific circuits, Fink and others argued that seizures are necessary and that these probably act through the release or inhibition of some endocrine factor, such as cortisol. Such thinking was almost openly derided at one point, but recent clinical trials of mifepristone have thrown the spotlight back on the dynamics of cortisol. This drug developed by the Roussel firm as an abortifacient, which also acts to cut cortisol output in the brain, was reported in early 2002 to be potentially effective in psychotic depression.[99]

It is far from clear that the results of ongoing trials with mifepristone will be sufficiently robust to warrant its development as a treatment, but this hint of efficacy from "an ECT in pill form" is intriguing for the light it sheds on the field. Were mifepristone successful for psychotic depression, its marketing would make it clear that melancholic or endogenous depressive disorders of this type are in fact a different illness from the what commonly passes as depression today. Most Prozac, Zoloft or Paxil-responsive depressions, which in the 1980s would have been regarded as anxious or neurotic depressions, would respond to neither mifepristone or ECT, while conversely none of the SSRIs has ever been shown to be effective in melancholia. If mifepristone were licensed for depression, what then would happen to the range of other conditions currently treated with SSRIs.

Would mifepristone transform these states into mythical mental illnesses? And if it did, would researchers on TMS and VNS be undertaking studies on these mythical illnesses or on mifepristone-responsive depressions? A bow to Thomas Szasz in the wings might be appropriate. Yet the following should also be noted: The range of disorders called in the last decades anxiety or depression often have psychosomatic features, and sometimes are determined entirely by social factors. Yet the disorders in this range almost certainly have more biological roots than is often recognized. The channeling of TMS and VNS down a "depression" route has probably owed a great deal to pharmaceutical company efforts to make depression the cash cow it became in the 1990s.[100] It may well be that these treatments are better suited to anxiety than to depression.

The mefipristone, DBS and VNS stories however also bring out some disturbing aspects to the new commercialism in the physical therapies of depression. Where once antipsychiatry activists railed against what they claimed was an establishment conspiracy to defend ECT, both academics and patients are now facing a world in which there is no incentive for the proponents to new therapies to concede that their procedures entail any risks, and every chance that only selective data will be published in ghostwritten articles.

It may not be possible to lift the academic gaze above the new commercialism to ask questions such as whether the real split is between seizures and stimulation, or between efforts at harmonization or enhancement on the one side and therapeutics on the other. When physical treatments like DBS were initially applied to Parkinson's disease clear brain circuits were sought. But this did not necessarily mean that those involved in the field were seeking to attack the root of the illness. Many researchers readily conceded that all they may be doing is to produce compensatory responses, or indeed inducing further brain dysfunction, in order to balance out the original disturbance, whatever that might be. For instance in Parkinson's Disease, the stimulation of the sub-thalamic nucleus produces therapeutic effects but does not do so by correcting the initial abnormality. The effect is to produce a compensatory lesion that, as it were, rebalances the system rather than corrects the problem.

A preparedness to induce a therapeutic disturbance is at the heart of treatment with ECT also. But this medical mindset is entirely alien to the mindset of electrotherapeutics, which from the early days of the nineteenth century[101] through to Alpha Stim has been all about trying to restore or induce harmony in the electrical fields of the body. In this, electrotherapeutics, old and new, resembles nothing so much as magnetism and Mesmer's Society of Harmony.

In the case of DBS for depression the language has been all about correcting the problem and immediate pleasurable responses rather than inflicting a therapeutic disturbance. In so far as this is the case, recent developments in brain scanning open up new intriguing prospects for treatment. If turning brain areas on and off by direct stimulation can produce benefits, it is quite likely that with new fMRI scans subjects could be trained to turn these same brain areas on and off by means of neurofeedback[102]. It seems increasingly clear that subjects who can see areas of their brains light up on brain scans in real time can learn to activate or deactivate these same areas just as we can learn to increase or decrease our heart rates once we are given feedback.

Neurofeedback seems to have just as much likelihood of working as invasive DBS. But history is not reassuring that we will take the less invasive route. After all biofeedback was a demonstrable success in the 1960s but we opted instead for treatment with pharmaco and psychotherapies for a range of conditions from anxiety to hypertension.

But if neurofeedback can produce equivalent effects to DBS, this perhaps points up a fundamental divide between the convulsive therapies and other electrotherapies, which is that seizure induction by neurofeedback is not an option. For the foreseeable future, while these new therapies may secure a place for themselves, they will not be a replacement for ECT.

There have been efforts from the start of the convulsive therapy era to replace ECT. Even Cerletti hoped to isolate a hormone changed by ECT, which could be given instead. Fluorothyl-induced seizures and then MMECT had a vogue. The literature on TMS, VNS and DBS since then often explicitly positions these approaches as a means to replace ECT. The worry has to be that in the new medical marketplace, dominated by

either pharmaceutical or device corporations, the marketing power of the mega-companies has created a situation in which less effective treatments can drive out better treatments – as the story of the SSRIs perhaps demonstrates.

In sum, time will tell whether another chapter in the history of shock therapy is being written today or not. The history of the last sixty years has been a history of successive attempts to improve ECT. All have failed. The treatment that Cerletti described in 1938, plus a few modifications around muscle relaxation and wave form, is still with us today, and a row of bright ideas about magnets, non-convulsive applications of electricity and the like have not succeeded in making patient care better or safer. It remains to be seen if the current crop will provide more convincing alternatives.

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