Throughout history, medicine has been governed by the question: "What can we do?" Technical limitations set the parameters for medical decision-making, limiting doctors to the procedures and therapies that were available to them. Additionally, medicine has always been governed by the second, more important question: "What ought we to do?" In addition to the many effective therapies that medicine offers, there are now technologies and therapies that are not de facto practical, appropriate, or ethical. It is now necessary to make complex decisions about cost and benefit, social availability of care, and difficult issues regarding ethics and morality. This change in emphasis on decision-making is most evident in the transformation of psychosurgery over the past century.

Psychosurgery as a term conjures up striking images of neurosurgical procedures from the early- to mid-1900s. It is interesting to note, however, that psychosurgery existed long before the advent of the leukotomy (popularly known as the frontal lobotomy), a procedure that is associated with that period. There is archaeological evidence that holes were drilled into human skulls as long as 5000 years ago in Europe and Northern Africa. This procedure, referred to as trephination, was a technique that is believed to have fit into the psychological and spiritual understandings of that time, and yet was probably used for a clinical purpose even at such an early period in history.

In modern medicine there were a few early attempts at psychosurgery in the early 1900s, but most were met with harsh criticism and disregard. When the much-respected Egas Moniz and his colleagues performed the first prefrontal leukotomy at the Santa Marta Hospital in Lisbon, Portugal, on November 12, 1935, psychosurgery was launched into the popular domain and was catapulted down a path of unchecked experimentation and implementation. This path led to tens of thousands of these procedures being performed without adequate research demonstrating the safety of the procedure or a substantial benefit to the patient. Current perception is that these procedures were being performed secretly on state-hospital patients who were involuntarily committed, but in fact public opinion was so favorable at the time that patients were voluntarily undergoing the procedures at private hospitals as well.

Although the history of psychosurgery is dominated by the story of the leukotomy, it is important to note that appropriate research was being performed during the same period on other psychosurgical procedures. Progress in the field of psychosurgery was largely overshadowed by the public’s reaction to leukotomy.

Egas Moniz and the Rise of Psychosurgery

Egas Moniz was a prominent Portuguese neurologist who had received acclaim for his development of cerebral arteriography several years prior to his development of the prefrontal leukotomy. Although it appears that Moniz may
have influenced some peers to nominate him, his work on cerebral arteriography garnered consideration from the Nobel Prize committee on two occasions. Yet while Moniz was receiving credit for his arteriography work, his quest for recognition took a new turn at the Second International Neurological Congress in London in 1935. At this conference Moniz heard John Fulton and Charles Jacobsen present a study of 2 chimpanzees that displayed modified behavior after receiving surgically created frontal lobe lesions.\textsuperscript{32} Coupled with the growing scientific support for theories about cerebral localization, Moniz immediately saw an opportunity to enter medical history. After this conference he wasted no time in applying this new theory of behavior modification to humans who had no other therapeutic hope at a time when no psychiatric medications were yet available; this was the birth of the prefrontal leukotomy.\textsuperscript{33}

Initially Moniz instructed his surgical partner, Almeida Lima, to inject pure alcohol into the white matter of the anterior aspect of the frontal lobes. The alcohol would destroy neurons but was soon determined to be too imprecise, so Moniz then developed the “leukotome,” a device that functioned as a neurosurgical apple-corer.\textsuperscript{9} A wire loop on the end of a metal probe could be rotated, cutting axons in the target region. A simplified explanation of Moniz’s motivations can be constructed from some of the popular theories in neurology and psychology to which Moniz subscribed. Moniz thought of the prefrontal region of the brain as the psychic center of the person, Moniz also believed that earlier research supporting the inability of neurons to regenerate could be extrapolated to mean that neurons could not change. Thus, a person who had such “faulty wiring”\textsuperscript{2} as in schizophrenia or depression, would never change on his or her own, but possibly could be cured by severing the neurons responsible for such behavior. This theory speaks to Moniz’s total belief in organic medicine and his disregard for psychiatric therapies such as hypnosis.

Six months after the conference in London, Moniz and Lima began their clinical trial of the prefrontal leukotomy procedure. They performed these procedures on 20 individuals, and reported “seven recoveries, seven improvements, and six unchanged” patients.\textsuperscript{2,22} This would be a very small sample size by today’s clinical trial standards, but at the time the results appeared quite enticing. Moniz’s initial trial resulted in no deaths or serious morbidity, something that could not be said for some of the other treatments available for psychological disorders, such as insulin coma or electric shock therapy. Thus, the leukotomy looked as if it might prove to be a viable alternative to these other treatments.

Psychological evaluation of these patients following their treatment was somewhat subjective, but it showed improvement of a portion of patients with affective disorders such as anxiety or depression. Less convincing results were presented regarding patients with schizophrenia. The results on patients with affective disorders were convincing enough for several physicians and surgeons around the world to put the therapy into substantial use, and Moniz eventually received the Nobel Prize in 1949 for his contribution of “immense importance […] for the problems of psychiatric treatment.”\textsuperscript{26}

The 2 physicians most responsible for promoting the use of the leukotomy were Walter Freeman, a neurologist, and James Watts, a neurosurgeon practicing in Washington, DC. Together, Freeman and Watts began performing leukotomies in 1936, and using their modified technique performed approximately 600 of these operations. Their technique was adapted by neurosurgeons around the world. Further modification of the leukotomy resulted in “open” techniques, in which larger openings were made into the skull so that more adequate visualization and thus more accurate lesion placement could be achieved.

By 1949 it was estimated that 10,000 leukotomies had been performed in the US, with similar numbers collectively in England and Wales.\textsuperscript{32} Psychosurgery was standard practice in the medical culture of the time. The leukotomy was met with mixed reactions in the scientific literature, yet many who did not subscribe to the opinion that it was a therapeutic miracle believed that it was still a necessary avenue of experimentation. This belief led to further clinical trials and other types of psychosurgical procedures. Much of the clinical research was criticized for lack of proper experimental design or statistical integrity, yet the response of psychosurgery advocates of the era was to use this objection as reasoning for why early research showed less than perfect results, rather than as an actual criticism of the motives for psychosurgery. Experimentation continued, and other types of selective lesion operations were developed.

One might ask how a procedure that is now so ethically and therapeutically taboo came to favor so easily. At the time there was such a void in the treatment of the mentally ill that any option providing therapeutic hope was used even without thorough investigation. Publications reported preliminary case studies to the public, and the large population of mentally ill patients and their families rushed to their doctors seeking out the new treatments. This type of public influence is similar to today’s pharmaceutical advertising to the general consumer, in which portions of the public come to doctors’ offices requesting procedures or drugs without full knowledge of the ramifications of such requests.

\textbf{Psychoactive Drugs and the Decline of Psychosurgery}

In the 1950s there was growing acknowledgment that the popularity of the leukotomy was largely due to the lack of therapeutic alternatives for psychological pathologies, as well as to the Nobel Prize conveyed upon Moniz. These affirmations took the place of the scrutiny of clinical trials and scientific research, and there was a growing body of public doubt concerning the procedures.

Neurosurgeons thought of the procedures as imprecise and potentially dangerous, and psychologists thought of them as ineffective and unnecessarily invasive. In addition it was revealed that these psychosurgical procedures were not being used solely as a last resort; in fact, there were reported cases in which little investigation was used before the operations were performed.

The perception of psychosurgery was already changing as psychoactive drugs were introduced into therapeutic use. In 1954, the US Food and Drug Administration approved chlorpromazine for the pharmaceutical market. This antipsychotic drug was effective in controlling psychotic epi-
Physicians could finally treat psychotic patients effectively using chlorpromazine as well as reserpine, another psychoactive drug. Once these alternative therapies were available, the perception of psychological treatment was forever changed.

Before the introduction of psychoactive drugs, a favorable outcome for a patient with schizophrenia was simply a type of emotional sedation. Psychoactive drugs such as chlorpromazine not only sedated patients but also decreased delusions and hallucinations. Psychiatrists finally believed “like other doctors in that [they] had a treatment that really worked” for psychiatric disorders such as schizophrenia. Suddenly a therapy such as the leukotomy that offered an overall decrease of the amplitude of emotion in a patient seemed like a much less desirable therapeutic option.

In 1954, chlorpromazine had been prescribed to about 2 million people in the US. This led the way for the development and approval of other antipsychotic drugs, such as lithium and haloperidol, to be developed and approved, and it soon became clear that these pharmaceutical therapies were safer and often more effective than the surgical procedures that had been so widely used in the previous decades. By 1972, 90% of patients with schizophrenia were treated with psychoactive drugs such as chlorpromazine or reserpine. In the years since the advent of psychoactive drugs, many new products have come onto the market. Early derivatives of the chlorpromazine class of drugs were used as the first antidepressants. Research on psychoactive drugs has since been vigorous, leading to the currently used antidepressants and antipsychotics. These new drugs offer more hope to patients and have fewer and fewer side effects for people who suffer from psychiatric disorders. Yet even in 1954 when chlorpromazine represented only the beginning of psychoactive drug therapy, the future of psychosurgery was already being challenged.

In 1967, the most prominent remaining proponent of the leukotomy, Freeman, performed his last procedure at Herrick Memorial Hospital in Berkeley, California. Freeman disrupted a cerebral vessel during the procedure, resulting in the patient’s death. Freeman’s surgical privileges were removed at his last venue for performing the leukotomy, and his retirement from psychosurgical practice paralleled the decline of psychosurgery from public favor.

The Current State of Psychosurgery

After the decline of the leukotomy, the term “psychosurgery” was equally avoided. Psychosurgical procedures continue to be performed to this day in the US and other countries, and although some clinicians believe that it is underused, it remains a very small subset within the category of functional neurosurgery. There are operations that are reminiscent of the leukotomy in their goals, yet much more sophisticated in execution. These operations include the limbic leukotomy, subcaudate tractotomy, anterior internal capsulotomy, and cingulotomy. Neurosurgeons can create very minute and accurately placed lesions in the brain using stereotactic techniques coupled with either standard surgical lesioning devices or radiosurgery. But there is also a vast array of new surgical therapies that offer treatment for conditions from intractable epilepsy to OCD and depression. Some of the surgical techniques that are currently being explored include the use of electrical stimulation of the vagus nerve and deep brain nuclei.

Vagus nerve stimulation currently is used as adjunct therapy for patients with epilepsy who do not respond to other therapies. Despite some success of VNS therapy in the treatment of epilepsy, much is still unknown about how VNS actually produces its effects. There is some similarity between the lack of knowledge of how VNS works and the lack of understanding that was present during the early days of psychosurgery. However, unlike historical psychosurgical procedures, VNS for the treatment of epilepsy has undergone rigorous testing and proof of efficacy as part of the US Food and Drug Administration approval process.

With the apparent success of VNS therapy in the treatment of one neurological disorder, physicians and researchers began investigating the ability of VNS therapy to treat other disorders, including depression, anxiety disorder, obesity, pain, cognition and memory deficits, Alzheimer disease, and migraine headaches. Depression was one of the first areas targeted for a clinical trial, after physicians noted positive mood changes in patients with epilepsy who received VNS therapy. This investigation has led to a mix of case studies and prospective trials examining the application of VNS therapy for conditions ranging from depression to bipolar disorder, and even appetite suppression.

Perhaps one of the most ethically tantalizing trials of VNS involved memory and cognition. Studies in animals revealed that VNS resulted in increased focus and alertness after a period of treatment. Additionally, it was recognized that patients with epilepsy receiving VNS therapy showed increased recognition memory. These results have prompted researchers to investigate VNS therapy as an antagonist to the progression of Alzheimer disease, but this area of research has not yet been fruitful.

Deep brain stimulation technology has also made a foray into the field of psychiatric disease, including diseases such as Tourette syndrome, depression, and OCD. Deep brain stimulation techniques have been more palatable to ethical oversight than traditional psychosurgery because they are relatively noninvasive and are reversible by turning off stimulation or removing the device.

Deep brain stimulation therapy was used to treat OCD by initially targeting one of the traditional surgical locations for lesion procedures, the anterior limb of the internal capsule. This procedure has demonstrated long-lasting benefits in some patients in small trials and case reports. Other locations such as the ventral caudate nucleus have been used as therapeutic targets as well for patients with intractable OCD.

Following the few reports of the success of DBS as a treatment for a psychiatric disorder such as OCD, further clinical trials have included patients with Tourette syndrome, and depression. The spectrum of psychiatric disorders that are treated with DBS continues to grow.

The Advent of Neuroethics

The development of new technologies in the treatment of neuropsychiatric disorders has brought the understanding
of neuroscience to a threshold in which one must proceed with much caution. In the history of psychosurgery, ethics took a backseat to experimentation due to the lack of therapy for mental illness, and now there is the potential that ethics may take a backseat to the tantalizing prospects of newly found technologies. This void of ethical consideration is being addressed by a new field called “neuroethics,” a discipline that seeks to answer ethical questions raised by the new technologies that are becoming available everyday. The field was described by Al Jonsen, an organizer of one of the first conferences on the subject, as an “unexplored continent lying between the two populated shores of ethics and neuroscience,” a statement that reflects the need for ethical discussions. However, there are significant amounts of ethical work that have been produced already, and these bodies of work can provide a starting point for the ethical dialogue.

In 1972 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was founded, and it immediately addressed the issue of patient consent. The commission found that an institutionalized patient was not competent to give consent to a psychosurgical procedure. The same commission issued a set of guidelines dealing with the scientific justification of psychosurgical research and informed consent. In addition, the guidelines stated that psychosurgery had not been proven appropriate for children, and that further research in general was required to show the safety and efficacy of specific psychosurgical procedures.

There are already opinions regarding the nature of psychological conditions and their treatments, and these opinions can provide some groundwork for the development of neuroethics. The spectrum of opinions is extremely wide, with one extreme suggesting that disease is organic and the mind is spiritual. According to this opinion, psychological ailments are diseases that are not confinable to the abstract brain; thus, psychosurgery and other physical therapies are ineffective in the treatment of such disorders. The other extreme suggests that all aspects of personhood can be modified, improved, or repaired by physical alteration of the brain. If behavior is rooted entirely in neurochemistry, then it can be modified by surgery or pharmacology. This school of thought seeks to use surgery and other therapeutic methods to counter crime, violence, and other social problems.

These types of considerations and the multitude of ethical opinions that already exist in the use of surgery and other therapies can be considered the ethics of neuroethics. The term neuroethics is what Roskies terms “the neuroscience of ethics,” which deals with the caveat that one of the bases of moral thought is the distinctly human activity of reasoning and emotion. Neuroethics therefore deals with the circuitous issue of a therapy having an effect on the very basis of ethical reasoning.

It follows that psychosurgery, functional neurosurgery, and other neuropsychiatric therapies that modify human emotion and behavior can change the way ethics are viewed. One can imagine the dilemma posed by a society that has overwhelming scientific control of its understandings of ethical and moral behavior. Kantian models of metaphysics take on entirely new dimensions when the basis of moral and ethical behavior can be manipulated surgically or chemically. What happens when medical therapies can change “who we are”? At the first conference devoted to neuroethics in 2002, Don Kennedy pondered the ramifications of developing “architectonics of ethical decision making.” Kennedy’s statement addressed the possibility of humans having physiological control over their ethical perspectives. Certainly there are extremely important ethical, legal, religious, and other consequences of this type of thinking. Neuroethics is only beginning to seek out the questions to ask.

Legal implications abound, given that our society already avoids prosecution of those who are determined to be mentally incompetent. What happens then when the desire to steal or harm is redefined as a brain dysfunction that can be modified? Will the legal system reach a point where all crime is considered organically caused, and thus immune from current concepts of prosecution and justice? Guidelines must be formed regarding human experimentation, given that psychological research using animal models is quite limited. Within experimentation and clinical application, concepts of consent and competence can be challenged in conditions such as depression and anxiety that are considered physical pathologies that cloud perception and can be physically remedied.

What happens to a society built upon concepts of the individualistic mind and spirit? In a relativistic society, how does one determine what emotional state is pathological and what is normal? This is only a sampling of the questions that are surfacing in neuroethics. These questions are numerous and complex, and they strike to the very core of many of the currently accepted models of ethics, accountability, and the self.

Neuroethics is still a young field, and there is not yet a definitive set of questions that need exploration by scientists and ethicists. Nevertheless, the difficult process of deciding what questions and answers need to be explored will determine the future of neuropsychiatric medicine and ethics as a whole.

In retrospect, it is interesting to ponder whether Egas Moniz would have traveled down the road of the leukotomy he had known that he was not simply searching for a treatment of thought seeks to use surgery and other therapeutic methods to counter crime, violence, and other social problems.


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