

# History of Biological Treatments in Psychiatry in the 20th Century

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**Abstract:-** This year commemorates a century since the discovery of insulin, a substance that in 1927 (only 6 years after its synthesis) was used by Manfred Sakel to treat patients with schizophrenia and other psychotic diseases. The insulinic shocks were in fact one of the revolutionary milestones and drivers of biological treatments in psychiatry.

**Objective -** When celebrating the 100th anniversary of the discovery of insulin and its importance in the revolution of treatments and imposition of Psychiatry as a medical specialty, this article seeks to review the literature on this treatment and its positioning in the history of biological treatments throughout the twentieth century.

**Methods -** Non-systematic review of the literature on the theme under study. Search was done in the PubMed database, with the following keywords: shock therapy; seizure therapy; biological treatment; insulin therapy.

**Results -** The most used treatments throughout the 20th century were insulinic shocks, malariotherapy, camphor-induced convulsions and electroconvulsive therapy. The use of these treatments was based on the principle that seizures were beneficial for alleviating symptoms and curing various mental illnesses, including schizophrenia. Although there are several reports from this time about the recovery of patients submitted to these techniques, electroconvulsive therapy was in fact the first biological treatment to present cohesive and consistent positive results.

**Conclusion -** At a time when the etiology of psychiatric pathologies was unknown, the use of insulin shocks and induction of seizures for the treatment of schizophrenia and other psychotic diseases revolutionized the treatment in psychiatry. With the discovery of psychotropic drugs, namely antidepressants and antipsychotics, most of these techniques have gone into disuse and nowadays only electroconvulsive therapy is used in specific cases.

**Keywords:-** Convulsive treatment; history of psychiatry; Sakel's method; electroconvulsive therapy component; formatting; style; styling; insert.

## I. INTRODUCTION

Throughout the history of mankind we can find several descriptions of mental disorders, whose treatments have varied over the centuries according to the religion and customs of the time. In prehistory it was considered that mental illness was caused by the power of the Gods and Demons, the individuals who exhibited symptoms of mental ill-health were subject to religious rituals or abandoned to their own fate. In ancient

Greece, the idea that patients should be treated with kindness was begun, physical exercise and exposure to fresh air and sunlight were part of the treatment. If patients did not improve, flogging was one of the suggested treatments. In the Middle Ages, mental illness was once again associated with divine entities, with the sick being subjected to exorcisms, placed on the margins of society, or even killed. Until the 19th century, despite some advances in medicine and in the way of facing mental illness, there were no significant developments in the treatment of patients with mental illnesses. These were kept in nursing homes, isolated from society and only received simple care and some social support, since there was no effective or direct treatment to this type of pathologies (1).

In the first decades of the 20th century there was a great evolution in the way of understanding and treating mental illnesses, with the development of medicine and the acquisition of knowledge about the human body and mind. In the early 1920s several advances emerged in the treatment of schizophrenia and other mental illnesses and biological treatments began to be used to attenuate symptoms and try to cure these patients. It was at this time that Doctor Julius von Jauregg instituted malariotherapy for the treatment of neurosyphilis, on the grounds that fever and seizures would be beneficial for the improvement and even remission of symptoms. This discovery initiated several studies that culminated in convulsive therapies, which later originated electroconvulsive therapy. In parallel with these therapies, in 1921 insulin was discovered and years later was used by psychiatrist Manfred Sakel to cause severe hypoglycemia and consequently changes in the state of consciousness in order to attenuate symptoms resulting from psychiatric disorders. These treatments were used for a few decades, going into disuse with the discovery and institution of psychotropic drugs, such as antipsychotics and antidepressants.

In this article, and in a year commemorating the centenary of the discovery of insulin, we discuss the discovery and use of insulin shocks, as well as other biological treatments in the treatment of psychiatric disorders throughout the twentieth century.

## II. METHODS

A non-systematic review of the literature on the theme under study was conducted. This research focused mainly on articles published in the PubMed database, with the following keywords: shock therapy; seizure therapy; biological treatment; insulin therapy.

### III. RESULTS (REVIEW OF LITERATURE)

Studies related to convulsive therapy in psychiatric practice in the early twentieth century were considered innovative, such that in the first half of the twentieth century these methods were widely used around the world. Among the various techniques available, the results were highlighted by the results obtained, the insulinic shocks, the malariotherapy, the convulsions induced by cardiazole and the electroconvulsive therapy. Lobotomy also appeared at this time, standing out from the other techniques because it is not based on the induction of seizures.

#### A. Insulinic shocks

In the 1920s, the use of insulin shock was a major advance in the treatment of schizophrenia and other psychoses. The insulin had been discovered in 1921 by two Canadian doctors, Frederick Banting and Charles Best, but it was only in 1927 that Manfred Sakel, at the time interned at the Lichterfelde Psychiatric Hospital in Berlin, first used it in Psychiatry. He used insulin injections to cause a superficial coma in a morphine-dependent woman, with a significant recovery<sup>(2, 3)</sup>.

The assumption of this technique was that insulin would act as an adrenaline antagonist, whose elevation would be the cause of many psychiatric symptoms. In 1930, Sakel began perfecting what became known as the "Sakel technique", first at the Neuropsychiatric Clinic of the University of Vienna, and then in 1934 in the United States, to escape the Nazi regime. In September 1933, this technique was officially publicized and acclaimed.

The treatment itself lasted several weeks or months, with patients receiving daily insulin injections. Normally, a coma lasting 30 to 60 minutes was sought, but if the patient developed hemodynamic instability, the session was immediately suspended. The interruption was performed with administration of a warm glucose solution through a nasogastric tube or intravenous glucose administration. The insulin dose was increased daily, inducing increasingly profound states of unconsciousness, until the patient was considered to have achieved the "maximum benefit", at which time insulin would be gradually reduced. On average, between 30 and 50 episodes of coma were obtained<sup>(4)</sup>. Insulin shock was more effective in cases of schizophrenia, especially in those with the catatonic subtype and in the first two years of disease. It has also been successfully used in patients with delusional disorders (a situation formerly referred to as paranoia).

In the 1930s, doctors at the New York Veterans Administration Hospital reported that patients who woke up from an insulin-induced coma "often express a sense of being reborn". Several works carried out in the United States of America, between 1939 and 1942, helped in the worldwide expansion of this technique. According to a 1939 study published by Ross and Malzberg in the American Psychiatric Association of a sample of 1039 patients treated with insulin shocks, 12.9% were considered recovered after completion of treatment; 27.1% improved significantly; and 25.3% showed slight improvements. That is, 65.4% showed some degree of improvement, results higher than those obtained with shocks

with Cardiazole, another technique used at the time<sup>(5)</sup>. Another study published this year included 82 cases of schizophrenia treated with insulin shock. Treatment averaged 44.3 days, 106 hours of stupor and 2 hours of coma per patient. In this study, 31 to 38% of patients were considered recovered, 4 to 5% showed great improvement, 15 to 18% improved but relapsed before 8 months, and 32 to 39% showed no response<sup>(6)</sup>.

The initial enthusiasm for this technique was followed by the gradual decrease in its use, especially after several studies in the 1960s and 1970s showed that the improvements obtained were, in most cases, temporary. The benefit risk was being called into question, and there is evidence that some of the side effects of this technique were quite serious, including obesity, brain lesions with dysarthria, motor and sensory aphasia, monoplegia, facial paralysis and hemiplegias. The estimated mortality rate was 0.5 to 1%, and hypoglycemic encephalopathy was the main cause of death<sup>(7)</sup>.

#### B. Lobotomy

Archaeological findings, such as cave paintings, suggest that since antiquity, in various parts of the world, surgical procedures (making small openings in the skull) were used in an attempt to free people from "madness". Several centuries later, in the 1930s, Carlyle Jacobsen, studying the function of the different brain areas, found that after the destruction of the frontal and prefrontal cortex by lobotomy, there were changes in the behavior of chimpanzees, the animals became less aggressive, without apparent impairment in memory or intelligence.

These results were corroborated by Neurologist John Fulton who performed complete removal of the frontal lobes in two chimpanzees. Based on these experiences, neurology professor Egas Moniz developed lobotomy for the treatment of severe obsessive-compulsive psychoses and disorders in patients with repetitive thoughts who presented devious behaviors. The procedure consisted of the interruption of nerve fibers that join the frontal and prefrontal cortex to the thalamus through a technique called leukotomy. Several holes were opened in the skull through which an instrument (leukotome) was used, with which the brain fibers with laterality movements were cut. Egas Moniz reported inconsistent results with this procedure, finding decreased symptoms mainly in restless and anxious patients. It therefore proposed that this procedure should be reserved only for cases resistant to other forms of treatment<sup>(8, 9, 10)</sup>.

Later, neurologist Walter Freeman and neurosurgeon James Watts applied and perfected the technique by using it in several patients in the U.S., giving rise to the "Freeman-Watts Standardized Procedure." In this procedure, access to the prefrontal lobe was performed through the orbit, lasted about 30 minutes and required only local anesthesia, not requiring hospitalization. In 1949, Dr. Egas Moniz received the Nobel Prize in Medicine for his contribution to prefrontal leukotomy, which gave greater credibility to the procedure and contributed to its global dissemination.

In the early 1950s, movements against lobotomy emerged, justified in the scarcity of scientific evidence and

calling into question its real efficacy, since the only large-scale evaluation (Columbia-Greystone project) did not demonstrate clear positive effects of lobotomy. Ethical questions associated with the procedure were also raised, because it caused irreversible changes in the brain, personality and emotional life of patients. The technique was abandoned in favor of more humane methods of treatment, especially with the appearance of antipsychotic and antidepressant drugs, which proved to be quite effective<sup>(8, 9)</sup>.

### C. Malariotherapy

At the beginning of the 20th century syphilis was the main cause of dementia, and there is no available treatment capable of reversing the general paralysis typical of the quaternary form of this disease. At that time, Australian physician Julius von Jauregg found that some patients improved after episodes of high fever and seizures. In 1917 he decided to use malaria-contaminated blood in nine patients with chronic paralysis for advanced syphilis, causing high fever and seizures in the expectation of achieving symptomatic improvement. The results were in line with the expected, aiming at complete remission of symptoms in half of the patients and a considerable improvement in the remaining patients<sup>(11, 12)</sup>.

In 1927, Dr. Julius von Jauregg was awarded the Nobel Prize for the discovery of malariotherapy or malaria-induced fever, which at the time was considered an innovative treatment. This discovery revolutionized the approach of syphilis paralysis in several European countries, with the construction of specific sites for the creation of anopheles mosquitoes to be used by hospitals. There were wards where the mosquitoes were fastened to the patients, so that they were bitten and consequently infected. After some time to perform this treatment, it was concluded that the febrile peaks every 3 days, were the most effective, because they did not cause dehydration (which happened with the daily febrile peaks) and lead to a greater reduction of symptoms compared to febrile peaks of 4-4 days. Thus, only fever mattered and the blood of infected patients was used to transmit the disease to other people who needed treatment. Understandably this form of treatment has been abandoned over the years, notably since the 1960s, with the development of antibiotics and antipsychotics<sup>(11, 13)</sup>.

### D. Cardiazol-induced seizures

A technique developed by Ladislaus von Meduna in 1934 for the treatment of schizophrenia and affective psychoses. A trained neuropathologist, he began working as a psychiatrist in the 1920s, and found an antagonism between schizophrenia and epilepsy. It conducted post mortem studies on the brains of these patients, finding differences in glial cells of patients with schizophrenia (decreased glia) and epilepsy (increased glial cells), suggesting the existence of a biological antagonism between the two diseases. Unaware of Sakel's work, he then began the use of convulsive therapy as a form of treatment for schizophrenia, at a time when this disease was considered immutable<sup>(14)</sup>.

In 1933, after performing animal tests, he found camphor (previously used by Paracelsus in the 16th century to cure "lunatic" patients) as the most suitable substance to cause seizures. In 1934, he used this technique for the first time in

six patients with psychosis, obtaining good results. Later, with the improved technique and the discovery of new substances, he started using cardiazole (extracted from camphor) to induce seizures. In 1935, Meduna published the results of what she called "the first" twenty-six patients treated, reporting complete recovery in ten patients and significant improvements in three. Compared to insulin, cardiazol had the advantage of being cheaper and more reliable in inducing seizures, but unlike it, it had no antidote and seizures were stronger and more difficult to control, and it was not uncommon to observe dislocations and fractures<sup>(14, 15, 16)</sup>.

After a few years, Meduna concluded that the induction of convulsions with camphor or derivatives did not cure schizophrenia, but helped in faster remission of symptoms in acute cases of good prognosis. Over the years and the emergence of psychotropic drugs, this technique has gone into disuse, not being used at all in current times.

### E. Electroconvulsive therapy

The use of seizures for the treatment of psychiatric disorders had been studied since the early years of the 20th century, as can be seen throughout this study. However, electricity was only used for this purpose in 1938, through a technique developed by Ugo Cerletti and Lucio Bini, as a way to replace cardiazole in the induction of seizures. Cerletti studied epilepsy and together with Bini designed the prototype of the electroconvulsive therapy device. This device generated an electrical charge capable of providing energy to depolarize neuronal tissue, triggering a repeated production of generalized seizures<sup>(17, 18)</sup>.

By defining the parameters needed to apply electricity directly to the human scalp, they developed a reliable, easy-to-administer, and less-effective electrical seizure induction method. The first patient with schizophrenia treated with this technique performed 11 sessions and had remission of symptoms. In view of the success obtained, this method became the gold-standard for the induction of seizures, and the main biological treatment for mental disorders in the 1940s-1950s. This form of treatment, in its unmodified form, was, however, associated with several complications, such as fractures of the extremities and spine, so its use was progressively abandoned, being replaced by the modified version. It began to be used in the 1950s, with the use of barbiturates and muscle relaxants that allowed it to overcome the harmful effects of seizures. The fear that electroshocks could cause brain damage was contradicted by several studies that indicated that this technique may even increase neurogenesis in the hippocampus. With the introduction of antidepressants and antipsychotics during the 1950s and 1960s, this technique was no longer used as the first line, remaining as a treatment of choice for drug-resistant cases<sup>(17, 18)</sup>.

## IV. CONCLUSION

After the introduction of malariotherapy for the treatment of neurosyphilis in 1917, several physicians and scientists emerged who made a significant effort to find treatment for psychiatric pathologies (insulin shock, cardiazol-induced seizures and prefrontal lobotomy). These treatments were truly

revolutionary in that they proved much more effective than any other therapeutic intervention so far used. They spread rapidly throughout the world, opening a door of hope in the treatment of various mental pathologies. As knowledge grew, the ancient methods did not immediately become obsolete, and continued to be used and tested in different ways in nursing homes. However, they were phased out as their effectiveness was called into question, and many of their side effects became evident. Currently only electroconvulsive therapy continues to be used, in specific cases of disease resistant to other treatments, reducing the suffering of tens of thousands of patients. This technique, despite the stigma that still entails, has a well proven efficiency in several studies, with minimal side effects.

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