

Ugo Cerletti, *Pathologica* and electroconvulsive therapy

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Summary

Ugo Cerletti was the inventor of the electroconvulsive therapy (ECT) adopted in 1938 to treat schizophrenia. He had a robust education in anatomical pathology, which also left its mark on the journal *Pathologica*. Although his name is associated with several important moments and breakthroughs in the history of medicine, Ugo Cerletti's reputation has partly suffered from the same fate as his treatment. Electroshock was initially widely adopted, partly because of its low cost and relatively easy application, but with the advent of psychoactive drugs in the 1950s and 1960s, it subsequently came under ferocious criticism. Its fall from grace also affected to some extent the man who had invented it, though this seems hard to justify today.

Introduction

In 1934, A. Chiauzzi published an article in *Pathologica* describing a study on dogs entitled “*Experimental research on epilepsy using the Viale method*”¹. This significant work has often been mentioned in histories of psychiatry^{2,3}, and particularly in accounts of the developments that led to the use of electroconvulsive therapy (ECT) in humans. There are at least three reasons for the study's impact: 1. it demonstrated that the animals survived a flow of electricity through their central nervous system; 2. it became clear that an epileptic seizure could be triggered by the experimenters, who were able to control its intensity and duration (the so-called fractionated epileptic seizure); and 3. the study was conducted by one of Ugo Cerletti's assistants. It was Cerletti who commissioned the research, and it was Cerletti who – four years later – was the first, together with Lucio Bini (Rome, April 1938), to fine-adjust ECT for treating humans. But why was the study of epilepsy attracting so much interest in the 1930s? The reason lies in the assumption of a contrast between epilepsy and schizophrenia, which paved the way to possible therapeutic developments. This idea of a contrast was based largely on studies by a Hungarian psychiatrist Ladislav Meduna⁴, who claimed to have never encountered the two conditions in the same patient in all his years of clinical experience. He also reported having documented histological differences between the two disorders. He described an “*almost complete abolition of the function of the glia cells in schizophrenia and an increased proliferation in epilepsy*”. He also wrote that he had observed contrasting bodily features in the two types of patient (athletic in schizophrenia, leptosomic in epilepsy)⁵. These contrasting features brought to mind the Hippocratic paradigm that opposites cure opposites

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Conflict of interest

The Authors declare no conflict of interest.

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(*contraria contrariis curantur*). It is easier for us to see why if we consider that, around the same time, Julius Wagner-Jauregg was awarded the Nobel Prize for his studies on malaria therapy used to manage syphilis ⁶. Raymond Pearl had already documented a contrast between tuberculosis and lung cancer ⁷, contributing to laying the theoretical groundwork for research that ultimately led to the Canadian urologist Alvaro Morales ⁸ testing the use of the bacillus Calmette-Guerin (BCG) as a treatment for cancer of the bladder in the 1970s. In other words, there was a time when it was quite common to try to set one disease against another in an effort to identify effective treatments.

UGO CERLETTI IN THE HISTORY OF ANATOMICAL PATHOLOGY AND BEYOND

One of the reasons why Cerletti's assistant published his studies in *Pathologica* lies in the journal's importance, which was accentuated by the autarchic atmosphere of the period (even in the scientific world). Another lies in the fact that Cerletti was then a director of the neuropsychiatry clinic at the University of Genoa, the city where the journal was born (at the Ospedale Galliera). Cerletti's scientific training had focused largely on anatomical pathology, partly under the influence of the German school, as was typical at the time.

Alongside Augusto Tamburini in Italy, Cerletti's masters of scientific method and humanist culture were Franz Nissl in Heidelberg (before Cerletti graduated), and Alois Alzheimer in Munich (later on), alongside Emil Kraepelin (for Cerletti's clinical training) ⁹ (Fig. 1). Starting from the early years of the century and up until the above-mentioned study appeared in *Pathologica* in 1934 ^{1,10-32,37-45,46}, Cerletti's studies focused mainly on the histopathology of the brain, and on the glia in various normal and pathological conditions (Fig. 2). Among the latter, there are naturally numerous articles on neurosyphilis. This medical problem was of great concern in the early decades of the last century, and often discussed over the years in articles published in *Pathologica*. There was also no shortage of studies on the various cellular components of inflammation (Fig. 3), on pituitary gland and bone growth, on brain aging and on the role of the endothelium in the central nervous system. Knowing now what the older Cerletti's interests focused on the most, however, it is his studies on the histology of dementia, and his comments on Alzheimer's work on the microscopic roots of mental disorders that stand out ^{17,19,21,23,28,40,42}. Nevertheless, already from the early years of the century and up to 1910s and 1920s, Cerletti's curious gaze had been shifting towards horizons further away. He

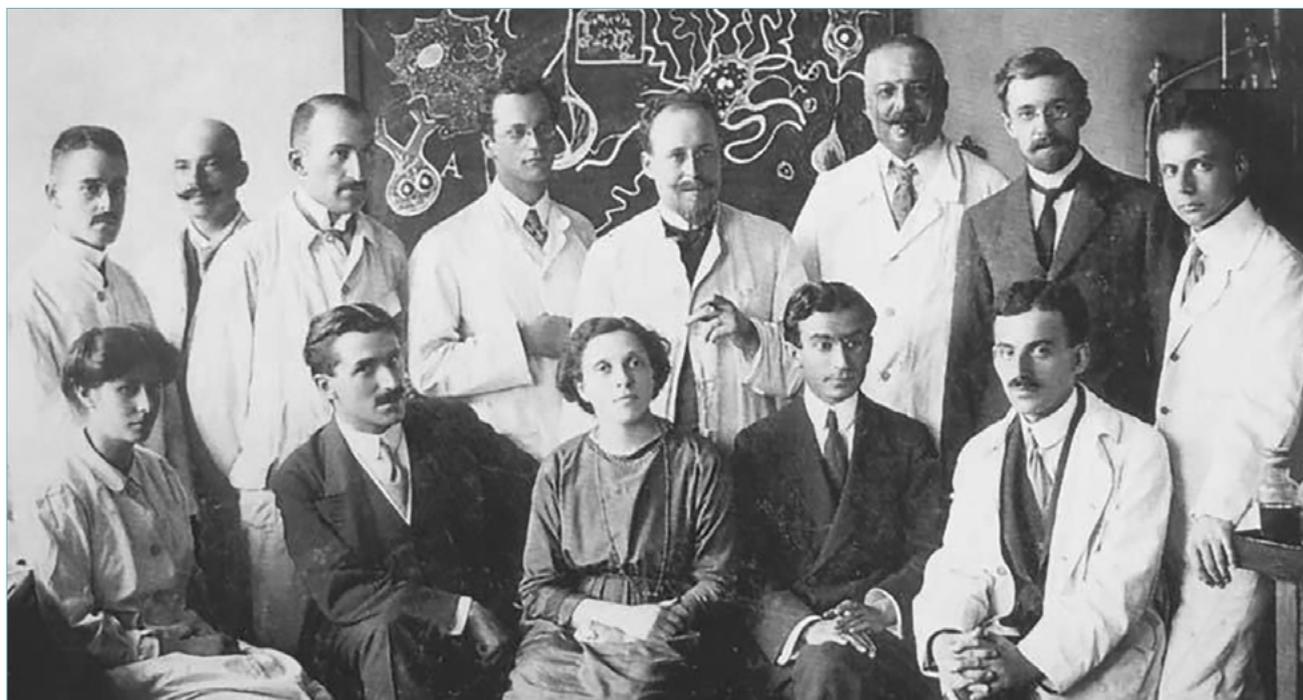


Figure 1. Front row, from left: Adele Grombach, Ugo Cerletti, unknown, Francesco Bonfiglio, Gaetano Perusini. Back row from left: Fritz Lotmar, unknown, Stefan Rosental, Allers (?), unknown, Alois Alzheimer, Nicolás Achúcarro, Friedrich Heinrich Lewy.

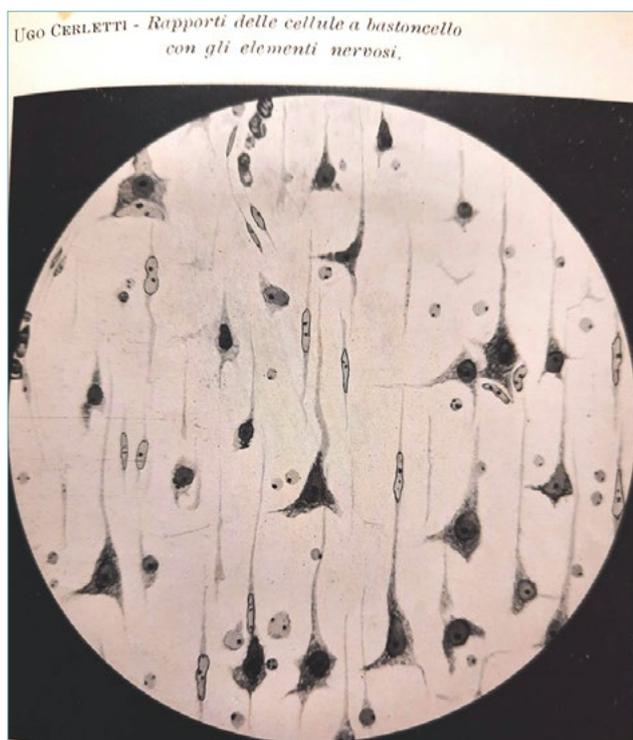


Figure 2. Cerletti U. Illustration in *Sopra alcuni rapporti tra le cellule a bastoncino e gli elementi nervosi nella paralisi progressiva* (from Cerletti, 1905) ¹⁰.

wrote works on “comparative psychiatry” (on hallucinations in dogs and cats under the effects of morphine) ^{27,39}, and studies on hysteria ¹². He also wrote studies on the effects of the hot southerly sirocco wind on the human mind, or on new dietary regimes ⁴⁴. Together with his friend Gaetano Perusini (the Italian neuropathologist and psychiatrist who contributed, maybe more than any other, to the discoveries made by Alois Alzheimer), Cerletti conducted investigations in the field of hypothyroidism in humans and animals. He soon produced some of the most important Italian works on the topic ^{13,16,31,43} and the thyroid remained one of his main scientific interests until he retired. His studies prompted a definitive shift away from the hereditary-degenerative view of endemic goiter, and clarified the importance of the environment and diet in the treatment of hypothyroidism.

Then the war came, and Cerletti became a medical captain. The war was also an opportunity for such a talented individual. First he came up with the idea of white camouflage clothing for the Alpini soldiers deployed in the mountains in winter – a solution promptly adopted by both the Italian and the Austrian armies. Then he designed such a novel delayed-action fuze

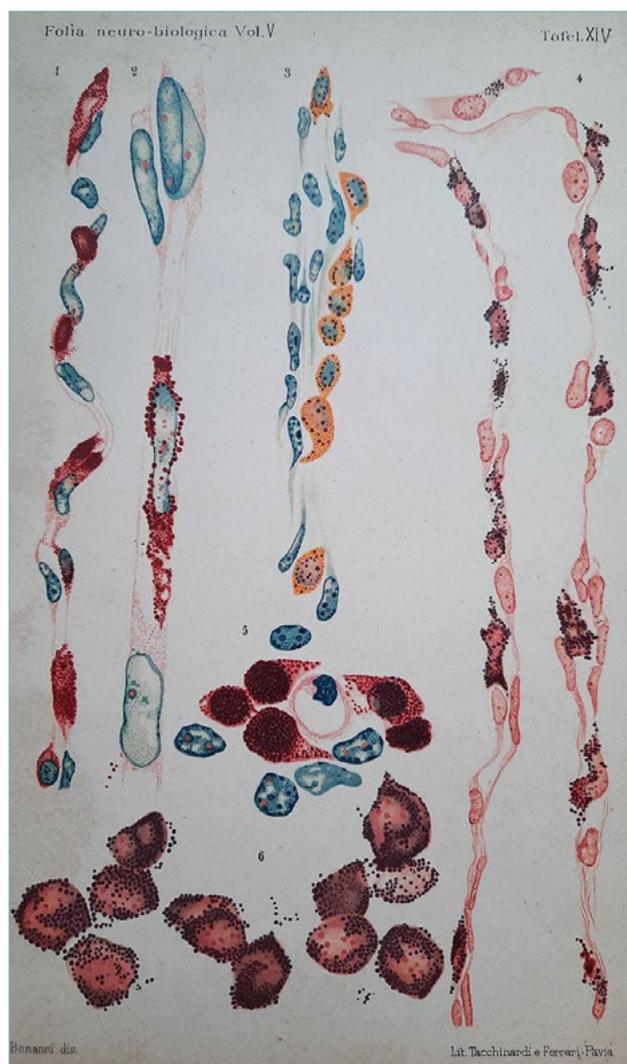


Figure 3. Mastcells of the olfactory bulb (U. Cerletti drawing).

that even the Allied armies were impressed ³³⁻³⁶. During the 1920s and 1930s, Cerletti continued to broaden the scope of his interests, intervening in the social sphere too. Even in the field of eugenics (a topic fashionable at the time), he took a stand, sometimes opposing the ideas that were tragically circulating in Europe ⁴⁷. These were the years when Cerletti was director of the laboratories at a large psychiatric hospital in Mombello (Milan), before he went to direct the neurology institute at the newborn University of Bari. The study published in *Pathologica* in 1934 (by which time Cerletti had moved to the University of Genoa) marks a turning point in his line of research. It is the first of a series of histological investigations on the effects of a flow of electrical current through the central



Figure 4. From *Le alterazioni istopatologiche del sistema nervoso nell'elettroshock*, (Cerletti et al., 1940)⁴⁹.

nervous system of various animal species^{48,49}. The animals were submitted to repeated treatments of various intensity and duration (from 125 to 220 volts for times ranging from one tenth of a second to several dozen seconds) to trigger an epileptic seizure. Then their neural tissue was examined to assess the site and extent of any damage. The evidence of nuclear pyknosis was described and photographed (Fig. 4)⁴⁹, and great attention was paid to examining Ammon's horn. But there was never any sign of those sclerotic phenomena already commonly encountered at the time in patients with severe epilepsy. These studies occupied the second half of the 1930s and continued after Cerletti moved to the University Sapienza in Rome in 1937. Apart from mild edema of the grey matter, the experiments failed to document any clear, characteristic and repetitive histological damage in the cortex of animals sacrificed after receiving a 125V electric shock lasting one or two tenths of a second. Their results pointed Cerletti and

Lucio Bini (his closest assistant psychiatrist) towards the idea of conducting experiments on patients with schizophrenic disorders. By this time, they had presumably come to the conviction (though we cannot say for sure) that ECT could induce a "*synaptic structural simplification*", an invisible lesion that would only affect the most labile neurons, i.e. the latest to have formed. In other words, Cerletti suggested that with ECT "*only the morbid structural complexes are destroyed, with a return towards the mental condition that existed before the disease*". This recovery would be achieved by the epileptic seizures triggered by the electricity, and Cerletti claimed: "*We shall see, on reawakening, the meso-diencephalic action of the deep regions of the brain that protect an ancient vital instinct*"⁵⁰⁻⁶⁰. The concept raised great expectations that eventually became irresistible in a world of psychiatry (like Italy's in the second half of the 1930s) that lacked other means, was culturally disinclined to explore the possibilities of psychotherapy, and had no pharmacological weapons other than barbiturates. There was also a strong desire to go beyond other shock treatments in fashion at the time, such as those involving insulin (Sakel, in Vienna), cardiazol (von Meduna, in Budapest) and acetylcholine (Fiamberti, in Varese). These methods had proved scarcely effective and too expensive. ECT seemed to be the only alternative to traditional treatments, or lobotomy (prefrontal leucotomy), which had been gaining ground at the time – with Egas Moniz in Lisbon (who was awarded the Nobel Prize in 1949), and Fiamberti in Italy. There is also an element of chance in this story, in the part played by Cerletti's first accidental and subsequently systematic observation^{2,3,9} of the effects of the electrical charges applied to pigs at the vast Testaccio slaughterhouse in Rome. Cerletti discovered that the animals did not die, not even after prolonged applications to the temples of the city's electrical power supply. This led to his tests on humans in April 1938, which were documented by the press at the time, and in the essays of the scholar Roberta Passione, Cerletti's principal biographer^{2,3,9}. The publications in the years immediately after 1938 consist mainly of a lengthy series of articles and monographs charting how the experimental studies were abandoned, and replaced with clinical reports⁵⁰⁻⁶⁰. The indications for ECT were expounded, details were provided on the methods for administering the treatment and its duration, and various technical issues were covered (largely the outcome of work done by Cerletti's colleague, the psychiatrist Lucio Bini). The results of applying ECT were reported, without neglecting to describe the side-effects of the convulsions. The articles were written mainly in Italian and German, but the use of ECT quickly now spread further afield, and the *Electroshock Research Association* was founded

in the United States in 1944. The treatment's success was such that Cerletti was proposed more than once for a Nobel prize and was awarded several honorary degrees (by the Sorbonne in France, the Universities of San Paolo and Rio de Janeiro in Brazil, and the University of Montreal in Canada).

CERLETTI THE ORGANICIST. A PARTIAL JUDGEMENT?

Ugo Cerletti's name is inseparably attached to a time when the world of psychiatry, driven mainly by the former studies conducted by neurologists like Paul Broca, Korbinian Brodmann and Carl Wernicke, was focusing on seeking the anatomic-pathological grounds for mental disorders. Though never demonstrated histologically, the hypothesis that ECT had an effect on meso-diencephalic areas and on "pathological synapses" belongs to this organicist perspective. Alongside his interest in hypothyroidism⁶¹⁻⁶³, Cerletti persisted in pursuing this concept after the war⁶⁴⁻⁸⁵. He continued to defend his ECT, though he criticized its misuse and sometimes erroneous prescription. Even after retiring (Fig. 5), he carried on (at his own expense), having become convinced that he could isolate a neuromediator that he called *acroagonin*, which could be extracted from animals submitted to ECT and administered to psychiatric patients, thereby sparing them the side-effects of ECT^{65-67,70,72,74}.

Right from the 1930s, however, Cerletti had been well aware of the problems posed by mental hospitals, and of the influence of the environment on the recovery of the mentally ill. He modernized the neuropsychiatry clinic in Genoa, making it more welcoming and removing the bars from the windows⁹. He showed an almost prophetic streak when, in 1949 (20 years before the battles conducted by Franco Basaglia), he declared: *"Is it even possible, is it logical, is it reasonable for us to treat people who have lost their mind by making them live amongst others who have lost theirs too?"* This rhetorical question appears in an article Cerletti wrote and published in the journal *"Il Ponte"*, edited by Piero Calamandrei⁸⁶. It is worth rereading a few more lines of this article: *"These institutes are established and organized on radically wrong principles... tens of thousands of unfortunates who wait to be released from a terrible plight, contrary to the most elementary logic, which severely delays, or even prevents the desired recovery of their mental sanity. These huge wards annihilate the patients' personality. They cannot concentrate, take stock, put themselves to the test. They have nothing of their own, not even their chair, no personal items of furniture, no drawers or personal effects. How can they possibly find themselves again?"*

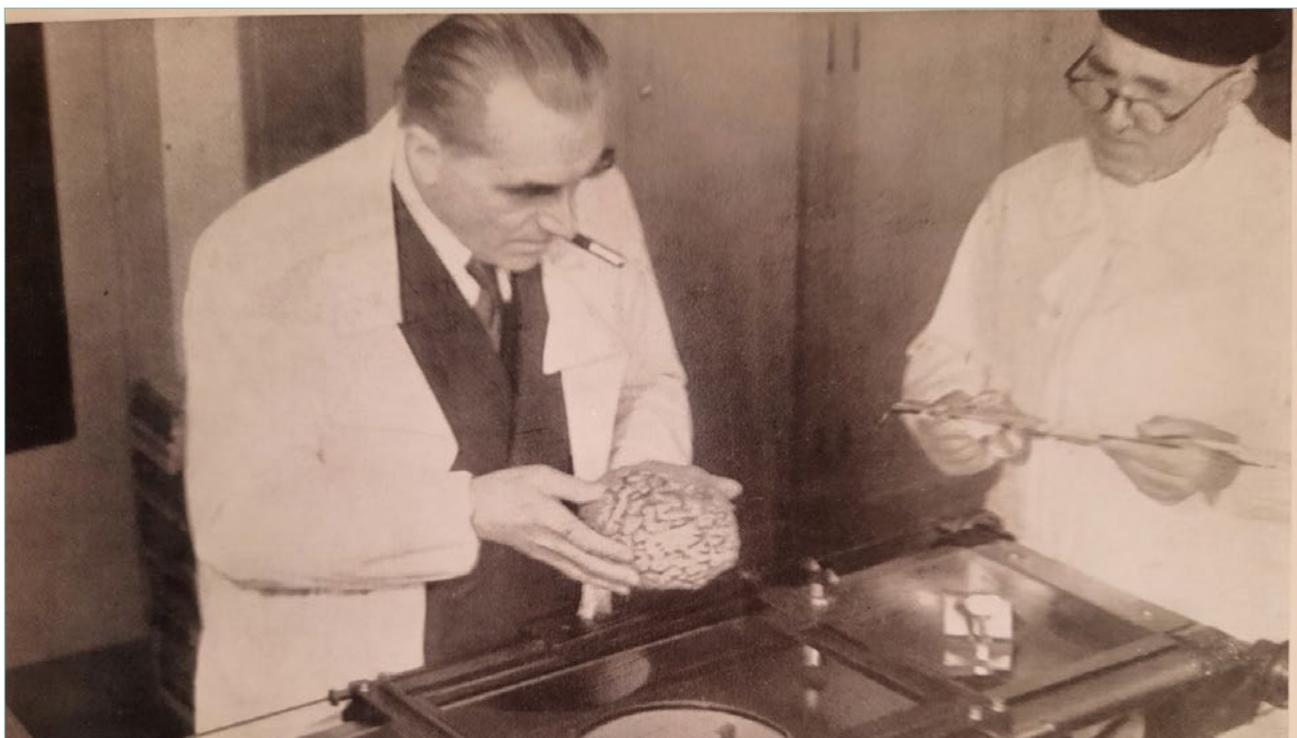


Figure 5. Ugo Cerletti in later years, but still professionally active.

Conclusions

ECT came under strong criticism, especially from important voices of modern psychiatry in the 1970s, but we can now look at it from a clearer historical perspective and reconsider its possible limited clinical applications⁸⁷. Although his name is associated with important moments and breakthroughs in the history of medicine, and he left his mark on the anatomic-pathological literature, Ugo Cerletti partly suffered the same fate as his ECT. The treatment was initially adopted with enthusiasm, though sometimes indiscriminately and erroneously, partly because of its low cost and relative “ease” of use. With the advent of psychoactive drugs in the 1950s and 1960s, ECT became the black sheep of psychiatry, casting a shadow over its inventor that today seems hardly justified.

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