


## ARTICLE

# Acroagonines: Ugo Cerletti's audacious attempt to place the neurophysiological effects of electroconvulsive therapy in vials

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## Abstract

In the years 1947–57, following a turbulent retirement, Ugo Cerletti, the father of electroconvulsive therapy (ECT) (1938), invested his energies in a new audacious project conceived as an extension of his ECT research. Forced to leave the direction of the Sapienza University Clinic, he got funds from the National Research Council of Italy to carry out his experimental activities, and founded a ‘Center for the study of the physiopathology of Electro-shock’ in Rome. The Center was aimed at studying liquid substances extracted from electro-shocked animals’ brains that Cerletti named *acroagonine* and injected into human patients. Inspired by coeval literature, Cerletti believed that electroshock efficacy was due to stimulating some homeostatic processes in the brain, specifically in the meso-diencephalic area (i.e. involving neuroendocrine response in the hypothalamic–pituitary–adrenal axis). Cerletti’s team wished not only to find these effects, but also to reproduce them. With this hypothesis, that proved ineffective, Cerletti anticipated intuitions on the neuroendocrine effects of ECT and the necessity for the development of psychopharmacology. In this article, I cross-combined previously unexplored archival materials stored at Sapienza University of Rome (‘ES Section’) with established bibliographic and archival sources.

**Keywords:** Acroagonines; ECT; Ugo Cerletti; Neuroendocrine; Psychopharmacology; Mental treatments

## Introduction

While the history of electroconvulsive therapy (ECT) has been widely explored internationally, acroagonine theory, formulated and tested by the father of ECT, Ugo Cerletti, in the 1940s–50s, has received scarce attention in scholarly work on the history of biological psychiatry and neurosciences. *Acroagonine* is the name Cerletti gave to liquid substances he conjectured to be produced by the brain under electroconvulsive treatment. Cerletti held these substances responsible for depressive patients’ recovery after ECT, and thus, he tried to extract them from electro-shocked animals’ brains to use as an injectable drug for psychiatric patients (Figure 1). With the exception of a few publications by Italian scholars,<sup>1</sup> acroagonines have been rarely mentioned in international works. Given ‘we know almost nothing about the neurological mechanisms of ECT’, acroagonines have been referred to by experts as ‘a

<sup>1</sup>Roberta Passione, ‘Electricity and life. Cerletti’s electroshock and the ‘Acroagonine’ theory’, in Giuliano Pancaldi and Paola Bertucci (eds), *Electric Bodies. Episodes in the History of Medical Electricity* (Bologna: Studies in History of Science, 2001), 265–87; Roberta Passione, ‘Italian psychiatry in an international context: Ugo Cerletti and the case of electroshock’, *History of Psychiatry*, 15, 1 (2002), 83–104; Andrea Piazzi, et al., ‘The history of Italian psychiatry during Fascism’, *History of Psychiatry*, 22, 3 (2011), 1–17.

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Figure 1. Acroagone vial.

pharmacological replacement for ECT... [that] did not work out'.<sup>2</sup> Acroagone research has thus been considered unsuccessful, irrelevant, and non-influential, driven by the goal of pharmacologically emulating the mechanisms of ECT.

Not only does common historiography on psychopharmacology neglect acroagone research, it also pays little heed to ECT's role in the birth of psychotropic drugs.<sup>3</sup> Even if ECT is currently subject to a historiographic reevaluation, the popular view still held is that psychopharmacology overcame the need for ECT<sup>4</sup>; indeed, it is generally believed that ECT and pharmacological treatments should be understood as two contrasting therapeutic approaches.<sup>5</sup> There have been, however, a few local exceptions to this viewpoint. Certain Italian scholars, for instance, have suggested that Cerletti opened 'the doors of the

<sup>2</sup>See Edward Shorter, 'Electroconvulsive therapy', in Conrad M. Swartz (ed.), *Electroconvulsive and Neuromodulation Therapy* (New York: Cambridge University Press, 2009), 167–179, 176.

<sup>3</sup>Acroagones are not mentioned in works like that by Thomas A. Ban, David Healy, and Edward Shorter (eds), *The Rise of Psychopharmacology and the Story of CINP*, 2nd edn (Budapest: Animula Publishing House/Collegium Internationale Neuro-Psychopharmacologicum, 2010). Cerletti never appears among the pioneers of psychopharmacology, for example, David Healy, 'Pioneers in psychopharmacology', *International Journal of Neuropsychopharmacology*, 1 (1998), 191–4.

<sup>4</sup>Jonathan Sadowsky, *Electroconvulsive Therapy in America, The Anatomy of a Medical Controversy* (New York, NY: Routledge, 2017).

<sup>5</sup>Edward Shorter and David Healy, *Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness* (New Brunswick, NJ: Rutgers University Press, 2007).

psychopharmacological turn in psychiatry'.<sup>6</sup> Others have gone further by saying that acroagonines were 'precursors to the psychopharmacology that would develop further after World War II'.<sup>7</sup> This is an interesting interpretation of the history of how psychopharmacological treatment has developed, which remains as yet unexplored.

There is another aspect of the acroagonine hypothesis that, even though cited by prominent historical sources, has not been fully investigated.<sup>8</sup> That is, acroagonine theory originated from the insight that mental disorders and treatments – particularly depression and ECT – must be understood in neuroendocrine terms. Accordingly, the neuroendocrine explanation of ECT, as well as neuroendocrine psychiatry, in general, were consistently defended from the late 1970s.<sup>9</sup>

As will be argued in this article, acroagonine theory has relevance for both the origins of psychopharmacology and the emergence of the neuroendocrine explanation of mental illness. Specifically, Cerletti emphasised the role of a precise brain structure, the diencephalon, in the action of ECT, and more specifically, he associated mood disorders with hormonal-hypothalamic dysfunction. Diencephalon localization received careful consideration in late-1950s psychiatry after it turned out to be a crucial intuition that led Jean Delay and Pierre Deniker to test chlorpromazine, an antihistaminic with limbic neural activity, on psychiatric patients. According to Francophone historiography,<sup>10</sup> Jean Delay was not only the initiator of contemporary psychopharmacology but also the originator of the diencephalon hypothesis, while Cerletti came after and acknowledged Delay's influence. This article attempts to refine such historical narrative, arguing that acroagonines, a neglected theoretical and research stage of twentieth-century biological psychiatry, though later proven false, paved the way for subsequent scientific insights and developments in contemporary psychiatry.

Along with other known archival and bibliographic sources, this article makes use of unexplored archival materials, herein named the 'ES Section' after the pen-marked abbreviations present on each of the binders, stored at Sapienza University of Rome. The ES Section is part of the Ugo Cerletti Archival Collection located at the Library of Human Neurosciences at Sapienza University of Rome, Italy, found in the New Historical Archive of the Child Neuropsychiatry Section. The ES Section consists of ten non-inventoried, unnumbered and unordered binders originally pen-marked 'ES', which were here given provisional and casual numbers under a preliminary inventory (herein 'Unit'). The records (miscellaneous print items, correspondence, notes, photos, drawings and other materials) are largely in Italian, are mostly dated between 1946–1958, and have been thus attributed, during this research project, to Ugo Cerletti's activities at the 'Center for the study of the physiopathology of electro-shock' at the National Council of Research of Italy, described hereafter. As far as is currently known, the ES Section is presumed to be the only collection of Ugo Cerletti's records on ECT research that remains in Rome, after two shipments of Cerletti's papers were sent to the USA by family following his death, in 1965 and 1972.<sup>11</sup> This Ugo Cerletti Collection, consisting of twenty-one boxes of archival records and six other folders of honours, is now held under the Menninger Historical Psychiatry Collections at the Kansas State Historical Society (KSHS) Archives in Topeka (Kansas, USA), having previously been stored at the

<sup>6</sup>Roberta Passione, 'Introduzione', in Roberta Passione (ed.), *Ugo Cerletti: Scritti sull'Elettroshock* (Milano: Franco Angeli, 2006), 45; Stefano Canali, 'Il Comitato Nazionale di Consulenza per la biologia e la medicina', in Raffaella Simili and Giovanni Paoloni (eds), *Per una Storia del Consiglio Nazionale delle Ricerche* (Roma: Laterza, 2001), 480.

<sup>7</sup>Piazzini et al., 'The history of Italian psychiatry', *op. cit.* (note 1), 258.

<sup>8</sup>Shorter and Healy, *Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness*, *op. cit.* (note 5), 286.

<sup>9</sup>Edward Shorter and Max Fink, *Endocrine Psychiatry: Solving the Riddle of Melancholia* (New York: Oxford University Press, 2010).

<sup>10</sup>Emilie Bovet, 'Biography of a brain structure: Studying the diencephalon as an epistemic object', in Kenneth S. Kendler and Josef Parnas (eds), *Philosophical Issues in Psychiatry III The Nature and Sources of Historical Change* (New York: Oxford University Press, 2015), 123–39; Emilie Bovet, 'Biographie du diencéphale. Revisiter l'histoire de la psychiatrie a travers le parcours d'une zone cerebrale', Thesis at the University of Lausanne 2012, available at the University of Lausanne Open Archive: <http://serval.unil.ch>.

<sup>11</sup>Correspondence, Lucio Bini's Collection, Box 2, Kansas State Historical Society Archives (herein KSHS Archives), Topeka, Kansas.

Menninger Foundation Archives. The KSHS Archives also store the related Lucio Bini Collection, consisting of two folders, one of which has been digitised and shared online. The KSHS Cerletti and Bini collections have been used as source material in producing this article.

A third Ugo Cerletti Archive, located at the Italian Historical Museum of War in Rovereto (TN) (Italy), is dedicated exclusively to a Cerletti's military invention he made while serving in the army in WWI, the delayed-action fuse, or *spoletta*. Since the Rovereto collection contains no records on his neuropsychiatric research, it has been excluded from this research.

This article used the author's translations of the original Italian archives. As an Italian native speaker, the author was aware of the interpretative difficulties of the task and hopes she succeeded in replicating Cerletti's tone and intention in English.

### The plight of a passionate mind

Following the very recent vote of the Superior Council of P.E. [Public Education], which granted no exception – admitted by the Law – to the retirement of Professors who have reached the age limits from their Institutes, I will have to leave the Clinic I lead at the end of next October.<sup>12</sup>

With this pencil-drafted note to the then President of the National Research Council of Italy (CNR),<sup>13</sup> Ugo Cerletti (1877–1963) (Table 1), the father of the celebrated ECT, that he and Lucio Bini introduced in 1938,<sup>14</sup> was expressing his deep sense of frustration. From his reference in the letter to 'the next October', and to research conducted in 1947–8, we may infer Cerletti wrote this around 1948. At the age of retirement, Cerletti started a turbulent and costly<sup>15</sup> legal battle that came to a negative end. Supported by his lawyer Mario Bracci, legal professor and dean of the University of Siena,<sup>16</sup> Cerletti strenuously fought against the then Minister of Public Education Guido Gonella, a prominent Christian Democratic deputy, who refused to extend Cerletti's position as director of the Clinic of Nervous and Mental Diseases at Sapienza University in Rome.<sup>17</sup>

Cerletti's experience was not isolated. In the post-war era, many academics were opposed to a law enacted during the fascist period, the so-called De Vecchi Law (1935). Previously, a restriction on the

<sup>12</sup>*In seguito al recentissimo voto del Consiglio Superiore delle P.I. col quale non si è concessa – secondo ammetteva la Legge – nessuna eccezione alla estromissione dai lor Istituti dei Professori che hanno raggiunto i limiti d'età, io dovrò lasciare la Clinica da me diretta, alla fine dell'Ottobre p.v. Questo accade nel momento in cui più attivamente furono le mie ricerche sulle 'Acroagonine' le quali hanno risultati sempre più incoraggianti in vari campi, e specialmente in diverse malattie mentali e in malattie nervose come la poliomielite acuta e altre forme di encefaliti, oltre a quella rabbica'.*

Ugo Cerletti to CNR President, Hand-draft, undated, ES Section, Unit 3, Child Neuropsychiatry Section, Library of Human Neurosciences, Sapienza University, Rome, Italy (hereinafter 'ES Section'). My translation.

See also Roberta Passione, *Ugo Cerletti: Il Romanzo dell'Elettroshock* (Reggio Emilia: Aliberti Studio Unipress, 2007), 22, n. 14.

<sup>13</sup>Gustavo Colonnetti (1886–1968) was president of the National Research Council of Italy (CNR) from 1944 to 1956. See: <https://www.cnr.it/it/presidenti>.

<sup>14</sup>The original ECT apparatus prototype is displayed at the Sapienza Museum of the History of Medicine in Rome. The Museum owns three original patents (Italy, France and Argentina) and two other patent applications (Germany and Great Britain) as well beyond other materials, including an acroagonine vial (see Figure 1, and note 89). See Elisabetta Sirgiovanni and Alessandro Aruta, 'From the madhouse to the docu-museum: the enigma surrounding the Cerletti-Bini ECT apparatus prototype', *Nuncius*, 35 (2020), 141–64: 159. See also Elisabetta Sirgiovanni and Alessandro Aruta, 'The electroshock triangle: disputes about the ECT apparatus prototype and its display in the 1960s', *History of Psychiatry*, 31, 3 (2020), 311–24.

<sup>15</sup>Notes of legal expenses, typewritten. Folder 'Limiti d'età', Ugo Cerletti Collection, Unit ID 36458, KSHS Archives, Topeka, Kansas, USA.

<sup>16</sup>Reasons of the acrimony between Cerletti and Gonella are unclear, but they may have been of political nature. Mario Bracci to Sapienza Dean, Siena 11 March 1949, Ugo Cerletti's Folder AS 597, Historical Archive, Sapienza University, Rome, Italy (hereinafter 'Sapienza Historical Archive').

<sup>17</sup>Passione, *Ugo Cerletti: Il Romanzo dell'Elettroshock*, *op. cit.* (note 12), 135, 149, n. 12.

**Table 1.** Key events in Ugo Cerletti's biography.

1877	Ugo Cerletti is born in Conegliano (TV), Veneto (Italy)
1900	Visiting student under E. Kraepelin and F. Nissl, in Heidelberg (Germany), and under P. Marie and E. Dupré in Paris (France)
1901	Graduates in Medicine and Surgery with Honors at Sapienza University, Rome (Italy)
1902–15	Research assistant in brain tissue pathology under E. Sciamanna and A. Tamburini at Sapienza University
1904	Research on endemic goiter with Gaetano Perusini in Northern Italy
1909–10	Visiting researcher under E. Kraepelin in Heidelberg (Germany), and under F. Nissl and A. Alzheimer in Munich (Germany)
1915–18	Serves in WWI and invents the <i>spoletta</i>
1919–20	Free lecturer at Sapienza University
1922	Director of the Neurobiological Institute, Psychiatric Hospital, Milan (Italy)
1924	Chair of Neuropsychiatry at the University of Bari
1928	Director of the Psychiatric Clinic at the University of Genoa
1933	Research on epilepsy and electricity
1935	Director of the Clinic at of Nervous and Mental Diseases Sapienza University, Rome
1938	First ECT test on a human patient, with Lucio Bini
1940	First publication on acroagonine theory
1947	Founds the ES Center in Rome, funded by the National Research Council of Italy
1948	Retirement from Sapienza University and continuing research activities as <i>fuori ruolo</i> professor
1957	The ES Center closes
1963	Cerletti dies in Rome

maximum working age that prevented professors from working beyond 70 years old was used to exclude dissidents of the fascist regime from Italian academia. However, the Constituent Assembly of Italy, established to draft the post-war Constitution in 1946, considered the norm unjust and re-fixed the limit to 75 years old for professors, like the previous Rava Law (1909).<sup>18</sup> The lower limitation was maintained for directors of institutes or university chairpersons, who could continue to serve in office only if of 'exceptional merit'. The press reported that, incredibly, of the sixty-two applications submitted by different faculties that year – among which was Cerletti's – all were rejected because the merit criteria they had to meet were too restrictive and 'naïve'.<sup>19</sup> Besides, the number of members required to pass the quorum (two-thirds of the Superior Council of Italy) was rarely present at the meetings. A witness reported that, of the scholars put forward, Cerletti got the most favourable votes.<sup>20</sup> 'After all, my electroshock has conquered half the world',<sup>21</sup> he remarked to Agostino Gemelli, while thanking him for his support of the application to continue working as a professor.

<sup>18</sup>The Spectator, 'Un problema psicologico: i limiti d'età', *Rassegna di Studi Psichiatrici*, XXXVII, (1948), 199–200.

<sup>19</sup>*Ibid.*, Silvio Negro, 'I vecchi ringiovaniti per meriti speciali', *Il Corriere della Sera*, 7 August 1948, 3; Ugo Cerletti Collection, Unit ID 36458, KSHS Archives. Francesco Giugni, 'I professori universitari al traguardo dei settant'anni', *Il Pensiero Medico*, XXXVII, 166 (1948).

<sup>20</sup>Francesco Severi, Letter to Guido Vernoni, Rome 3 July 1948. Ugo Cerletti Collection, Unit ID 36458, KSHS Archives.

<sup>21</sup>Ugo Cerletti, Letter to Agostino Gemelli, 19 June 1948. Ugo Cerletti Collection, Unit ID 36458, KSHS Archives.

From his notes, it appears Cerletti viewed the enforced retirement as ‘disturbing’.<sup>22</sup> Cerletti felt persecuted, alienated, and doomed to join the “‘dead” in science’.<sup>23</sup> The dismissal of his application had been a greatly humiliating experience, especially considering how he described his obsession for science and research from a very young age as ‘a true addiction’.<sup>24</sup> Besides this, as with many others, Cerletti had encountered and overcome tremendous difficulties in seeking to pursue his research during the war, including loss of assistants and lack of material resources.

‘This happens at the moment when my research on “Acroagonines” was most active’ – Cerletti complained to the CNR President in the above mentioned letter – ‘[and when acroagonines] have given increasingly encouraging results in various fields, especially in various mental illnesses and nervous diseases such as acute poliomyelitis and other forms of encephalitis, in addition to that provoked by rabies’. Cerletti had invested his hopes, energies and personal money<sup>25</sup> in this new audacious project conceived as an extension of his ECT research. With support from an academically powerful and charismatic professor of general pathology at Sapienza and leading figure at the National Research Council, Guido Vernoni (1881–1956),<sup>26</sup> and help from his long-standing friend and director of the Provincial Asylum *Santa Maria della Pietà*, Francesco Bonfiglio (1883–1966),<sup>27</sup> Cerletti founded a ‘Center for the study of the physiopathology of Electro-shock’ (ES Center). The CNR Presidency Council had approved the foundation of the ES Center at the Sapienza Clinic on 28 January 1947, allocating a yearly fund of 1 000 000 Lire<sup>28</sup> (around 20 000 euros as today). These funds were, for Cerletti, ‘an oasis in the middle of the desert of 50 years of hardship’.<sup>29</sup> This center and others, following a model of previous CNR centres established in 1929,<sup>30</sup> were intended to promote the rebirth of Italian scientific research after the Second World War.<sup>31</sup> In March,<sup>32</sup> CNR approved the proposal made by Vernoni and Cerletti to move the experimental activities of the ES Center from the Clinic, where Cerletti had been confined and left without patients, to the Provincial Asylum in Rome, led by his friend Francesco Bonfiglio.

### The acroagonine theory

The ES Center was aimed at studying extracted liquid substances from electro-shocked animals’ brains (especially, from pigs and sheep<sup>33</sup>) that Cerletti named *acroagonine* (referred to as ‘acroagonines’ or sometimes ‘acroagonins’ in English), or substances of high biological activity, ‘from the Greek *ἄκροσ*

<sup>22</sup>Ugo Cerletti, Letter to the University Dean, 20 April 1949. The entire material of correspondence and notes was stored in a Folder ‘Limiti d’età’, Ugo Cerletti Collection, Unit ID 36458, KSHS Archives.

<sup>23</sup>Ugo Cerletti (attributed to), Fuori Ruolo, Hand-drafted notes. The expression recurs also in Sui limiti di età per i professori fuori ruolo, Typewritten draft. Folder ‘Limiti d’età’, Ugo Cerletti Collection, Unit ID 36458, KSHS Archives.

<sup>24</sup>Ugo Cerletti (attributed to), Hand-drafted notes. Ugo Cerletti Collection, Unit ID: 36461, KSHS Archives.

<sup>25</sup>Passione, *Ugo Cerletti: Il Romanzo dell’Elettroshock*, *op. cit.* (note 12), 158, 170, n. 24.

<sup>26</sup>Guido Vernoni had established eleven CNR research centres in different Italian cities in the years 1945–7. See Stefano Canali, ‘Il Comitato Nazionale di Consulenza per la biologia e la medicina’, *op. cit.* (note 6), 458–512.

<sup>27</sup>See Elisabetta Sirgiovanni, ‘Electroconvulsive therapy applications on children in the 1940s: the Italian case’, *The Journal of ECT*, 37, 3 (2021), 152–7.

<sup>28</sup>Assembly Minutes, n. 43, 28 January 1947, Folder 5, CNR Presidency Council under Gustavo Colonnetti (1944–56), Central Archives of the State, Rome, Italy. See also Ugo Cerletti, ‘Sostanze di estrema difesa prodotte dall’Elettroshock (Acroagonine)’, Comunicazione all’Istituto Superiore di Sanità, 19 June 1947, in Roberta Passione (ed.) *Ugo Cerletti: Scritti sull’Elettroshock*, *op. cit.* (note 6), 131–44.

<sup>29</sup>Ugo Cerletti (attributed to), Typewritten drafts, undated, Ugo Cerletti Collection, Unit ID 36452, KSHS Archives.

<sup>30</sup>Riservata, Typewritten drafts, Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>31</sup>Canali, ‘Il Comitato Nazionale di Consulenza’, *op. cit.* (note 6).

<sup>32</sup>Assembly Minutes, n. 47, 28 March 1947, Folder 5, CNR Presidency Council under Gustavo Colonnetti (1944–56), Central Archives of the State, Rome, Italy.

<sup>33</sup>Albino Foglia to the University Clinic of Nervous and Mental Diseases, 6 June 1948, Handwritten letter, ES Section, Unit 3, Sapienza University, Rome. The letter reports that eighteen sheep costed 111 555 Lire.

(utmost) *ἀγών* (struggle).<sup>34</sup> Cerletti explored various terms from Ancient Greek (*istagonina*, *telagonina*, *cerlagonina*, etc.) before finding one that was suitable.<sup>35</sup> Mindful of the experience with the ECT apparatus prototype in 1939, which he accepted to be patented by Lucio Bini only – an event that later caused tensions between the two,<sup>36</sup> – Cerletti immediately patented the name in Italy in 1948,<sup>37</sup> and then in 1953, he applied to the German,<sup>38</sup> USA,<sup>39</sup> and UK<sup>40</sup> patent offices. Initially, he used the term ‘agonine’ as a generic label, believing these substances would possibly be found in other organs beyond the brain (*‘neuro-agonine, cardio-agonine, angio-agonine, pneumo-agonine, epato-agonine, etc.’*<sup>41</sup>). Cerletti’s hypothesis was that injections of these brain fluids in mental patients would produce the same – if not better – clinical effects of electroshock applications. The ‘success’ of ECT, for him, ‘could not be considered an end point, but indeed turned out to be the starting point of a series of difficult questions that arose due to their practical importance and their theoretical developments’.<sup>42</sup> He needed to understand how electricity affected ‘certain autonomic nervous centres with characteristic symptoms and with humoral and hormonal shifts’, mediated by alleged curative epileptic-like convulsions.<sup>43</sup> He also ‘thought to compare these particular modes of reactions in a large series of animals from very different species’,<sup>44</sup> a type of research that he and Lucio Bini had already explored since 1937.<sup>45</sup> They had so found that such ‘electric current... does not produce irreparable organic alterations in the brain’ – this is why Cerletti was supposing the presence of ‘diffusive... modifications’.<sup>46</sup>

Cerletti formulated as soon as 1940 his own hypothesis about the specific neurophysiological reactions to electroshock applications in a long monographic article entitled *L’Elettroshock*.<sup>47</sup> Cerletti believed that electroshock efficacy was due to stimulating some homeostatic processes in the brain, specifically in the meso-diencephalic area. His ideas came from Walter Cannon’s concept of homeostasis and other neuro-ethological research (e.g. Mikhail Kroll, Philip Bard and Curt Richter).

The idea of localising the epileptogenic region in the diencephalic area had been suggested before, in 1932, by Albert Salmon.<sup>48</sup> His assistant Giovanni Bollea and the physicist Angelo Manfredi showed, through studies on human corpses and dead and alive dogs, that the distribution of the electric current could affect subcortical structures.<sup>49</sup> For the occasion, Bollea and Manfredi built a two-electrode device detecting the potential difference in 1-cm extremes of the brains. They showed ‘that the electrical stimulus does not cross the brain from electrode to electrode, but that, having reached the stratum of the cerebrospinal fluid in which the brain is immersed, it follows this path... it passes especially into the large

<sup>34</sup>Anonymous, Pencil note, undated, ES Section, Unit 8, Sapienza University, Rome, Italy. See ‘Electroplexy explained?’ Annotation, *The Lancet* 251, 6489 (1948), 72–3.

<sup>35</sup>Ugo Cerletti (attributed to), Hand-drafted notes, Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>36</sup>Sirgiovanni and Aruta, ‘From the madhouse to the docu-museum’, *op. cit.* (note 14), 159.

<sup>37</sup>Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>38</sup>Registration in Germany is dated 23 May 1953. Studio Ing. Letterio Labocetta to Ugo Cerletti, Registered Mail, Rome 16 April 1954. Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>39</sup>United States of America Patent Office, 22 May 1956 (application 3 July 1953). Ugo Cerletti Collection, Unit ID 36466, KSHS Archives, Topeka, Kansas. See also Passione, *Ugo Cerletti: Il Romanzo dell’Elettroshock*, *op. cit.* (note 12), 170, n. 28.

<sup>40</sup>Great Britain and Northern Ireland Patent Office, London 25 September 1953. Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>41</sup>Ugo Cerletti (attributed to), Hand-drafted notes, Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>42</sup>Ugo Cerletti (attributed to), Hand-drafts, undated, ES Section, Unit 4, Sapienza University, Rome.

<sup>43</sup>Ugo Cerletti, ‘Fisiologia comparata dell’Elettroshock’, Report at the National Research Center, ES Section, Unit 6, Sapienza University, Rome.

<sup>44</sup>*Ibid.*

<sup>45</sup>Ugo Cerletti (attributed to), Hand-drafts, undated, ES Section, Unit 4, Sapienza University, Rome.

<sup>46</sup>*Ibid.*

<sup>47</sup>Ugo Cerletti, ‘L’Elettroshock’, *Rivista Sperimentale di Freniatria*, XVIII (1940); Passione, *Ugo Cerletti: Scritti sull’Elettroshock*, *op. cit.* (note 6).

<sup>48</sup>Albert Salmon, ‘Un centre végétatif épileptogène existe-t-il dans la région diencephalique?’ *La Presse Médicale*, 40, 20 (1932), 29. See Ugo Cerletti, ‘Conclusioni sulle acroagonine’, *Recenti Progressi in Medicina*, XIII, 3 (1952), 185–208.

<sup>49</sup>Giovanni Bollea and Angelo Manfredi, ‘Sulla distribuzione della densità di corrente elettrica nel cervello in relazione all’elettroshock’, *Il Lavoro Neuropsichiatrico*, I (1947), 419–22.

basal cisterns of the brain, it reaches the fourth ventricle, and through the aqueduct of Sylvius [it reaches] the third ventricle, where it acts on the surrounding vegetative centres'.<sup>50</sup> Cerletti's localization in the diencephalon was generic, although in 1951, he looked favourably on Alois Kornmüller's hypothesis on glia cells, which Cerletti had investigated with Franz Nissl in Heidelberg when, as a student, he was training in histopathology.<sup>51</sup> Plus, research on glia cells supported Ladislav Meduna's hypothesis of the antagonism of schizophrenia/epilepsy, which inspired shock therapies, ECT included.<sup>52</sup>

Yet, diencephalic localization contrasted with another popular idea, that is, that ECT stimulated the brain only cortically.<sup>53</sup> Cerletti's assertion that 'what is obtained electrically from the cortex can only be an echo' was proven by studies with EEG in electroshock applications.<sup>54</sup> According to Cerletti, not only loss of consciousness (e.g. shock, sleep, apnea, and coma), but the onset of consciousness itself had to be localised within the meso-diencephalic brain area, and not – like many other authors suggested – in the frontal cortex.<sup>55</sup>

Taking inspiration from Charles Darwin's remarks on emotions (especially the idea of a *syndrome terror-defence*),<sup>56</sup> Cerletti supposed that in a phase subsequent to the shock (the 'agony' phase), which he called 'counter-shock' or transition phase, the brain was secreting hormonal substances conducting a state of so-called general adaptation syndrome (GAS). Owing much to Cannon's physiology,<sup>57</sup> Hans Selye identified this pattern of responses under stress (i.e. alarm, resistance, and exhaustion).<sup>58</sup> Cerletti interpreted this state as a 'defence reaction against future exposure to the same stress'.<sup>59</sup> Other coeval references were Constantin von Monakow and Raoul Mourgue on terror neurosis, or Kurt Goldstein's 'catastrophic reaction'.<sup>60</sup>

Cerletti thought of a homeostatic balance in what would be later called the hypothalamic–pituitary–adrenal axis. This emerges from his drawings where a trauma or stressor stimulates the adrenocorticotrophic hormone (ACTH) and so cortisol production, then the adrenal gland is involved, and finally deoxycorticosterone and hyperglycemia are originated (Figure 2).<sup>61</sup> He stored another sketch of a pituitary gland (Figure 3).<sup>62</sup>

Finally, in Cerletti's imaginative mind, acroagonines were sort of 'vitalizing substances', secreted by the brain for hormonal balance, which permitted 'specific resistance' to less or more severe pathologies,<sup>63</sup>

<sup>50</sup>*Ibid.*

<sup>51</sup>Cerletti, 'Conclusioni sulle acroagonine', *op. cit.* (note 48), 200–5.

<sup>52</sup>Ugo Cerletti, La nascita di una terapia, Typewritten drafts, Ugo Cerletti Collection, Unit ID 36465, KSHS Archives.

<sup>53</sup>Cerletti, 'L'Elettroshock', *op. cit.* (note 47). Shorter and Healy, *Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness*, *op. cit.* (note 5), 46.

<sup>54</sup>Ugo Cerletti (attributed to), Quelques données de l'électro-encéphalographie en rapports à l'E.C., Typewritten drafts, Ugo Cerletti Collection, Unit ID 36465, KSHS Archives.

<sup>55</sup>Cerletti, 'L'Elettroshock', *op. cit.* (note 47), 74–98. See also Lamberto Longhi, 'Sintomi Psicici nella patologia delle formazioni della base encefalica, Parte Prima, Natura ed essenza dei sintomi psicici, Il problema della coscienza', Relazione al XIII Congresso della Società Italiana di Psichiatria, Roma ottobre 1946, *Rivista Sperimentale di Freniatria*, LXXII, I-II (1949), 3–34, ES Section, Unit 2, Sapienza University, Rome.

<sup>56</sup>See Charles Darwin, 'The expression of the emotions in man and animals, 1872', in F. Darwin, P.H. Barrett, and R.B. Freeman (eds), *The Work of Charles Darwin* (London: Pickering, 1989). Darwin is referenced by Ugo Cerletti, for example, in: Ugo Cerletti, 'L'Elettroshock', *op. cit.* (note 47), 103; Ugo Cerletti, 'L'Elettroshock', Congresso Internazionale di Psichiatria 1950, *Passione, Ugo Cerletti: Scritti sull'Elettroshock*, *op. cit.* (note 6), 190.

<sup>57</sup>Mark Jackson, 'Evaluating the role of Hans Selye in the modern history of stress', in D. Cantor and E. Ramsden (eds), *Stress, Shock, and Adaptation in the Twentieth Century* (Rochester, NY: University of Rochester Press, 2014).

<sup>58</sup>Hans Selye, 'The general adaptation syndrome and the diseases of adaptation', *The Journal of Clinical Endocrinology & Metabolism*, 6, 2 (1946), 117–230.

<sup>59</sup>Ugo Cerletti (attributed to), Speech International Congress of Psychiatry (1950), Handwritten Draft, Unit 7, Es Section, Sapienza University, Rome.

<sup>60</sup>Passione, *Ugo Cerletti: Il Romanzo dell'Elettroshock*, *op. cit.* (note 12), 114.

<sup>61</sup>Ugo Cerletti (attributed to), Drawing, Handwritten Draft, Es Section, Unit 7, Sapienza University, Rome.

<sup>62</sup>Ugo Cerletti (attributed to), Drawing, Handwritten Draft, Es Section, Unit 9, Sapienza University, Rome.

<sup>63</sup>Cerletti, 'Sostanze di estrema difesa', *op. cit.* (note 28), 166.



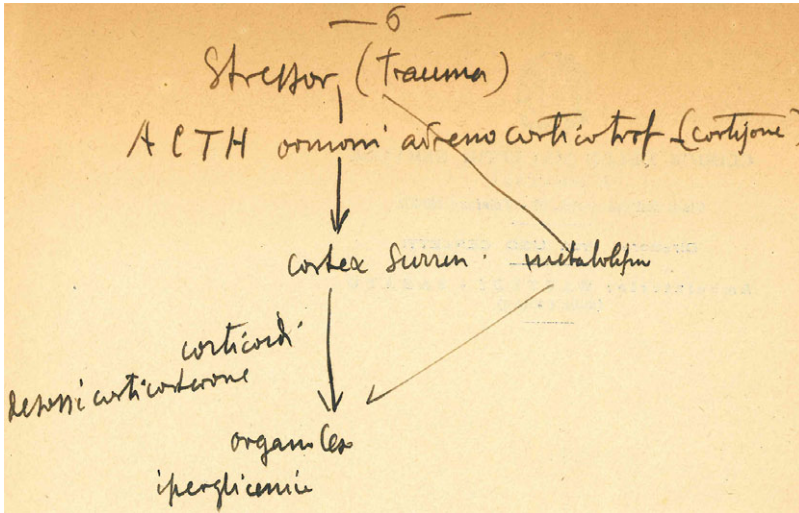


Figure 2. Action of the adrenocorticotrophic hormone.

from hair loss,<sup>64</sup> to psoriasis,<sup>65</sup> and terminal conditions,<sup>66</sup> beyond mental diseases. An analogous theory was that of ‘biostimulines’ postulated by the Russian Vladimir Petrovich Filatov for tissue grafts, a theory that Cerletti mentioned in different occasions,<sup>67</sup> or that of the conditioning of immune response by Serguei Metalnikov. In 1945, the effects of electricity on the diencephalon had been linked to the production of antibodies and antitoxins by injecting electro-shocked patients’ plasma and serum into other patients.<sup>68</sup> Other authors like Diego De Caro and Luigi Aru from Cagliari criticised Cerletti’s vitalistic interpretation, but shared this immunological-like hypothesis by focusing more on alleged bacteriological processes in mental illness and recovery.<sup>69</sup> Following research of the late 1800 and 1920s on infective properties of mental patients’ blood and liquor,<sup>70</sup> they decided to test the emulsions in the laboratory by using bacterial cultures. In 1948, following research on rabbits conducted by Cerletti’s assistant Mario Felici at the Roman Clinic, Ottavio Vergani and G. Garavaglia tested the link between ECT and specific antibodies (i.e. typhoid agglutinins) in Milan by vaccinating forty individuals against typhus and then electroshocking half of them; their conclusions from this work, however, were ambiguous.<sup>71</sup> In the years 1949–50, also Alfredo Poloni (Istituto Antirabbico Italiano) conducted research on liquor of electro-shocked subjects, another series of articles Cerletti stored.<sup>72</sup>

<sup>64</sup>Ugo Cerletti, Hand-drafted notes, 14 February 1957, Unit ID 36461, KHSH Archives.

<sup>65</sup>Agnese Guerrini Milone to Ugo Cerletti, Turin 17 August 1948, Unit ID 36465, KHSH Archives.

<sup>66</sup>Neri Accornero, Email Correspondence with the author, 7 April 2021.

<sup>67</sup>Passione, *Il Romanzo dell’Elettroshock*, *op. cit.* (note 12), 170: 30. An example is Cerletti, ‘Conclusioni sulle acroagonine’, *op. cit.* (note 48), 200.

<sup>68</sup>P. Doussinet and E. Jacob, ‘Importance du facteur humoral dans le mécanisme de l’action thérapeutique de l’électroconvulsion’, *Annales Médico-Psychologiques*, I (1945), 460–7. See Roberta Passione, ‘Elettricità e vita. L’elettroshock di Cerletti e le ricerche sulle acroagonine’, *Psicoterapia e Scienze Umane*, 4 (2002), 34–55.

<sup>69</sup>Diego De Caro and Luigi Aru, ‘Ricerche sperimentali sul potere antibatterico delle emulsioni di cervello di coniglio elettroshockato’, *Il Lavoro Neuropsichiatrico*, III (1948), 30–45. See Passione, ‘Elettricità e vita’, *op. cit.* (note 68), 53.

<sup>70</sup>Giuseppe D’Abundo, ‘Sull’azione battericida e tossica del sangue degli alienati’, *Rivista Sperimentale di Freniatria*, 18 (1892); Paul Von Gara, ‘Über die bactericiden kräfte der cerebrospinalflüssigkeit, sowie entzündlicher und nichtentzündlicher ergüsse der brust- und bauchhöhle’, *Klinische Wochenschrift*, 7 (1928), 2386–7.

<sup>71</sup>Ottavio Vergani and G. Garavaglia, ‘Elettroshock e anticorpi specifici’, *Minerva Medica* 39, 2, (1948), 1–8, ES Section, Unit 6, Sapienza University, Rome.

<sup>72</sup>ES Section, Unit 4, Sapienza University, Rome.

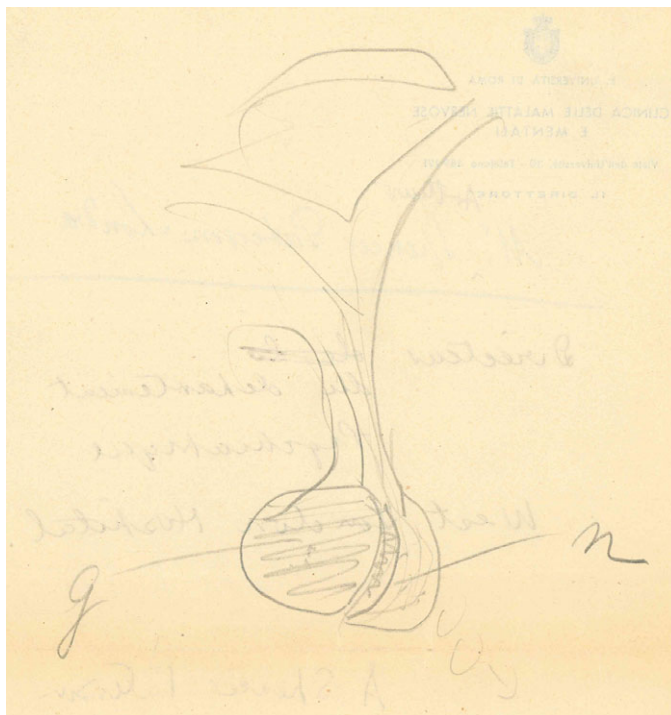


Figure 3. Pituitary gland.

For conceiving the acroagonine hypothesis, Cerletti and the others were actually overestimating some poor evidence coming from his team's experiments, which were showing partial recovery or delayed pathological manifestations in some acroagonine-inoculated rabbits and monkeys infected from fixed and aggressive viruses like rabies or polio.<sup>73</sup>

Cerletti's team wished not only to find these effects,<sup>74</sup> but also to reproduce them. Whereas with ECT one needed to 'repeat the applications over and over again',<sup>75</sup> Cerletti now wished to find some quicker, safer, and less terrifying means than electricity, or – as he used to say – an 'electroshock by proxy'.<sup>76</sup>

### Experimenting on acroagonines

Experiments on acroagonines had started officially on 14 March 1947.<sup>77</sup> A well-trained staff at the Roman slaughterhouse was daily electroshocking the hogs, and then carefully killing them so to extract their brains without any other modifications. The hogs' brains were brought to the Sapienza University

<sup>73</sup>Ugo Cerletti, 'Primo Congresso Internazionale di Psichiatria – L'Elettroshock (1950)', Parigi 1950, in Passione, *Ugo Cerletti: Scritti sull'Elettroshock*, op. cit. (note 6), 203–4. These tests were conducted respectively by Cerletti's assistant Ferdinando Accornero and by the paediatrician Luigi Spolverini; See Ferdinando Accornero, 'Ricerche sperimentali con emulsioni di cervello sottoposto a elettroshock', *Il Lavoro Neuropsichiatrico*, 3, 186 (1947). Luigi Spolverini, 'Acroagonine e virus poliomielitico', *Acta Paediatrica Latina*, 2 (1949), 1–31.

<sup>74</sup>See Giovanni Bollea and A. Manfredi, 'Sulla distribuzione della densità di corrente elettrica nel cervello in relazione all'elettroshock', *Il Lavoro Neuropsichiatrico I* (1947), 419–32.

<sup>75</sup>Ugo Cerletti (attributed to), Hand-drafts, undated. ES Section, Unit 4, Sapienza University, Rome.

<sup>76</sup>Ugo Cerletti (attributed to) Hand-drafts, undated, Ugo Cerletti Collection, Unit ID 36461, KSHS Archives.

<sup>77</sup>Report of Professor Cerletti's Activities 1947–8, ES Section, Unit 3, Sapienza University, Rome. The Report refers explicitly to the ES Center. Presumably, early preparations of the vials may have started a year before (see Figure 1).

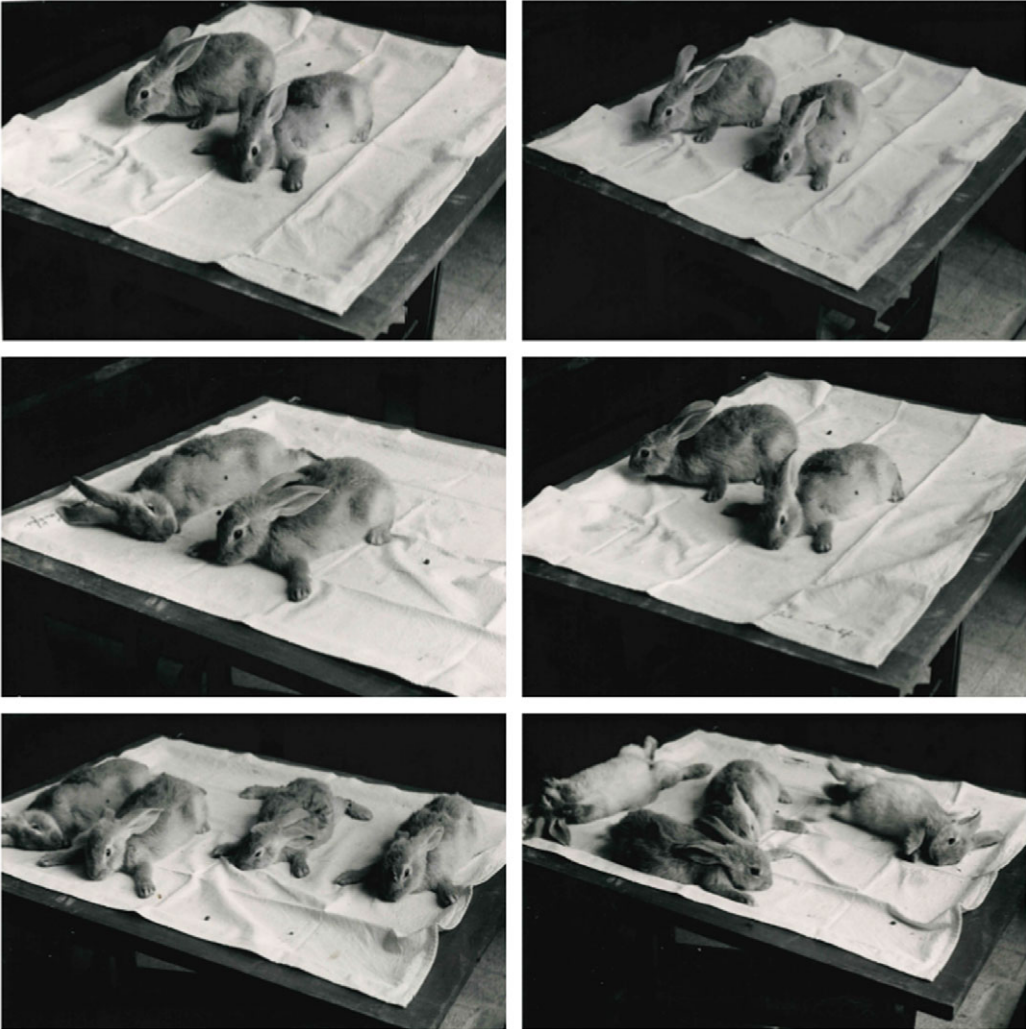


Figure 4. Experimental rabbits.

Hygiene Institute, where sterile emulsions were prepared. A team headed by Vittorio Puntoni, dean of the medical faculty and chair of hygiene at Sapienza, pulped the brains in mortar. They diluted them in aqueous suspension (10%) and 1% solution of phenol, a method already employed for rabies vaccines to avoid 'the delicate question of the toxicity of heterogeneous brain extracts'.<sup>78</sup> In 1950, French researchers (P. Gley, J. Rondepierre, and J. Oulès) used another method, that of insulin extraction.<sup>79</sup>

Before treating humans, Cerletti's team tested rabbits (Figure 4),<sup>80</sup> in order to see whether rabies-infected rabbits might have shown any effects from acroagonine inoculations, and then they injected a group of polio-infected monkeys donated by the Superior Health Institute.<sup>81</sup>

Afterwards, in a 1947 speech at the Superior Health Institute, Cerletti announced to have performed intramuscular injections on human subjects of these emulsions on thirty-six dysthymic inmates at the

<sup>78</sup>Cerletti, 'Conclusioni sulle acroagonine', *op. cit.* (note 48), 187; Passione, *Elettricità e vita*, *op. cit.* (note 68), 51.

<sup>79</sup>Cerletti, 'Conclusioni sulle acroagonine', *op. cit.* (note 48), 197–8.

<sup>80</sup>Rabbits are mentioned in the Report of Activities of the ES Center 1947–8, *Ibid.* Figure 4 is from ES Section, Unit 6.

<sup>81</sup>*Ibid.*

Sapienza Clinic and at the Roman asylum, and that he had injected himself as well.<sup>82</sup> Even if not properly randomised controlled trials, which would have made them among the first in the neurosciences, it is worth noting that twelve patients received initially (for about 3 days) emulsions from hogs' non-shocked brains (control group) and were then compared to patients treated only with emulsions from hogs' shocked brains (experimental group).<sup>83</sup> In some particularly resistant cases, ECT was administered some days after the shocked-brain-emulsions. It is unclear how the patients were assigned to one group or the other. However, Cerletti claimed to have obtained significant reactions in the experimental group, compared to the control group.<sup>84</sup> Cerletti's team stored graphs reporting observations on four patients<sup>85</sup> (a 81-year-old woman and three men), only one presumably belonging to the list of thirty-six, and a prescription on another,<sup>86</sup> that they treated with 2 cc, 5 cc, 10 cc emulsions. Notes on other six injected patients (three men and three women, aged from 19 to 35 years old, diagnosed depression or schizophrenia) were also stored.<sup>87</sup>

What Cerletti wished to get with his request to the CNR President in 1948 was financial aid for carrying out this research. Cerletti had noted that he wanted to obtain '200 vials of 5 cc' of these liquid substances (Figure 1) from each of 80 hogs he planned to request, and that his goal was to get '10 000 vials for clinical trials'.<sup>88</sup> He planned to use these vials for 'ten treatments in ten institutes'.<sup>89</sup> An Italian pharmaceutical company, in partnership with Rhône-Poulenc, rejected Cerletti's requests to produce the vials due to the difficulties in doing so and for other bureaucratic reasons.<sup>90</sup> A year later, Cerletti sought to enlist a European company – maybe a Dutch, but not an Italian or a German company – for the production.<sup>91</sup>

He also needed to hire some assistants now that, due to his forced retirement, he had been left without the ability to pay his collaborators from the Clinic funds. 'Cerletti and his collaborators, including in the first place Longhi and Fiume, as well as a host of doctors from the Clinic and the Psych. Hosp'. were 'working feverishly to dose the active power of the acroag. [acroagonines] in units as to be able to use them in ample tests in the various nervous and ment. [mental] diseases in the near future'.<sup>92</sup>

The faithful collaborators who joined the enterprise were Lamberto Longhi (1909–97), Sebastiano Gaetano Fiume (1913–2000), Giovanni Martinotti (1905–78), whose contracts were calculated to cost respectively 80 000, 50 000 and 46 370 Lire.<sup>93</sup> They 'up to now' had worked 'without any compensation from the center'.<sup>94</sup> Also Giovanni Bollea (1913–2011) and Bonfiglio's son Giovanni were involved, as

<sup>82</sup>Cerletti, 'Sostanze di estrema difesa', *op. cit.* (note 28), 150–8. A list of these patients' surnames is also stored in Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>83</sup>The team used control groups also when testing rabbits.

<sup>84</sup>See also M. Felici, 'Riassunto: Ugo Cerletti, Sostanze di estrema difesa prodotte dall'elettroshock', *Bollettino Sanitario della Tripolitania* V, 1–2, 1947, ES Section, Unit 1, Sapienza University, Rome.

<sup>85</sup>ES Section, Unit 8, Sapienza University, Rome. From a comparison of the names, only one of these patients presumably belongs to the list of the thirty-six patients.

<sup>86</sup>Trattamento di ECS (Emulsioni di Cervello Shockato), 1948, Typewritten/Handwritten Notes, Unit 3, ES Section. The name of the patient in the file was anonymized.

<sup>87</sup>Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>88</sup>Ugo Cerletti (attributed to), Pencil notes, ES Section, Unit 3, Sapienza University, Rome.

<sup>89</sup>*Ibid.* An acroagonine vial, supposedly the first preparation pen-marked 'Cerletti 1946', is displayed at the Sapienza Museum of the History of Medicine in Rome, although its originality is uncertain (Figure 1). See Sirgiovanni and Aruta, 'The electroshock triangle', *op. cit.* (note 14).

<sup>90</sup>Acon Schweiger, Farmaceutici Italia, to Ugo Cerletti, Letter, 6 May 1947. Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>91</sup>Ugo Cerletti to [Mario] Gérard, Letter, Typewritten drafts, Rome 12 May 1948. Ugo Cerletti Collection, Unit ID 36464, KSHS Archives.

<sup>92</sup>'Cerletti e i suoi collaboratori tra i quali in primo luogo Longhi e Fiume nonché una schiera di medici della Clinica e dell' Osp. Psych. stanno ora lavorando febbrilmente per dosare in unità il potere attivo delle acroag. Allo scopo domani di poterle adoperare in ampie prove nelle varie malattie nerv. e ment'. Anonymous, Pencil Note, undated, Unit 8, ES Section, Sapienza University, Rome. My translation.

<sup>93</sup>Ugo Cerletti (pencil notes) ES Section, Unit 3, Sapienza University, Rome.

<sup>94</sup>Ugo Cerletti to CNR President (note 12).

well as others.<sup>95</sup> Although at the time Cerletti was at loggerheads with his assistant Lucio Bini – the designer of the ECT apparatus prototype they co-invented – and with Lothar Kalinowsky,<sup>96</sup> his relationship with Lamberto Longhi was solid throughout his career.<sup>97</sup> Cerletti brought Lamberto Longhi with him from the University of Genoa to the Sapienza Clinic in Rome in 1936.<sup>98</sup> In Genoa, Longhi assisted Cerletti on studies about the endemic goiter,<sup>99</sup> whereas in Rome he was initially assigned to research on the effects of cardiazol/metrazol,<sup>100</sup> and then he joined electroshock studies. Twelve years later, in August 1948, instructed by Guido Vernoni, Cerletti delegated Longhi – ‘very diligent, insightful workmate and generous person’<sup>101</sup> – to withdraw a sum of money sent by the CNR (500 000 Lire) for the use of the ES Center.<sup>102</sup> Longhi’s presence in the activities of the center was definitely strong.<sup>103</sup>

As for the others, Sebastiano Fiume, a ‘voluntary assistant’ for Cerletti since 1939, had been confirmed with a paid position in Cerletti’s team from November 1943, in order to replace Ferdinando Accornero, another Cerletti’s assistant who was in the Army.<sup>104</sup> He continued to work there after Accornero’s return in 1947, when Accornero joined the research and performed the first acroagonine inoculations on rabies-infected rabbits.<sup>105</sup> Giovanni Martinotti, who had been working unpaid at the Clinic since 1938, got a post starting in 1946, and then was assigned to Vernoni’s lab to train in the ‘histopathological technique of the nervous system’.<sup>106</sup> Finally, Giovanni Bollea, who graduated in Turin and worked as a ‘voluntary assistant’ in Rome from 1939 on, had been appointed ‘assistant in charge’ in 1944.<sup>107</sup> A couple of years later, Cerletti – who with Sante De Sanctis contributed to the birth of child neuropsychiatry in Italy<sup>108</sup> – encouraged Bollea to train in children’s mental affections in Lausanne. Bollea was initially fully involved in the activities of the ES Center by providing relevant publications.<sup>109</sup> However, it was during his long stays in Paris, in 1948–9, that Bollea established strong links with Georges Heuyer, an international figure and Cerletti’s friend,<sup>110</sup> and at this time he was captivated by child neuropsychiatry.

### Discouraging results and the end of the acroagonine season

The expectations of the ES Center’s research were high. Already at the end of 1947, we have a record of the psychiatrist Umberto De Giacomo offering Cerletti to test this new treatment at the psychiatric hospital in Lecce.<sup>111</sup> During the same days Antonio D’Ormea, director of the Psychiatric Hospital in

<sup>95</sup>Cerletti, ‘Sostanze di estrema difesa’, *op. cit.* (note 28), 201.

<sup>96</sup>Sirgiovanni and Aruta, ‘From the madhouse to the docu-museum’, *op. cit.* (note 14), 159.

<sup>97</sup>Giuseppe Longhi, Conversation with the author and Livia Castelli, 7 July 2020, Rome.

<sup>98</sup>*Ibid.* See also Lamberto Longhi’s Folder AS 5074, Historical Archive, Sapienza University, Rome.

<sup>99</sup>Passione, *Il Romanzo dell’Elettroshock*, *op. cit.* (note 12). A. Costa and M. Mortara, ‘A review of recent studies of goitre in Italy’, *Bulletin of the World Health Organization*, 22 (1960), 493–502.

<sup>100</sup>Cardiazol was the term used in Europe, metrazol in the USA.

<sup>101</sup>Cerletti, ‘Conclusioni sulle acroagonine’, *op. cit.* (note 48), 198.

<sup>102</sup>Lamberto Longhi to Ugo Cerletti, Rome 21 August 1948, Typewritten Letter, ES Section, Unit 3, Sapienza University, Rome.

<sup>103</sup>Report of Activities 1947–8, ES Section, Unit 3, Sapienza University, Rome.

<sup>104</sup>Fiume Sebastiano’s Folder AS 10025, Historical Archive, Sapienza University, Rome.

<sup>105</sup>See, for example, Ugo Cerletti, ‘Centro di Studi sulla Fisiopatologia dell’Elettroshock, Attività svolta durante gli anni 1950–2’, *La Ricerca Scientifica* 10 (1953), 1756–66, Ugo Cerletti Collection, KSHS Archives, Topeka, Kansas.

<sup>106</sup>Guido Vernoni, Certification, Rome 10 July 1950, Giovanni Martinotti’s Folder AS 5309, Sapienza Historical Archive.

<sup>107</sup>Giovanni Bollea’s Folder A751, Personnel Archive, Sapienza University, Rome.

<sup>108</sup>Ugo Sabatello, Francesco Nardecchia, ‘La formazione in psichiatria infantile: tra storia e prospettive’, *Giornale di Neuropsichiatria dell’Età Evolutiva* 31 (2011), 29–36.

<sup>109</sup>In the years 1947–48, Bollea published seven articles on research conducted at the ES Center. Report of Activities 1947–8, ES Section, Unit 3, Sapienza University, Rome.

<sup>110</sup>Matteo Fiorani and Bollea, Giovanni, *Dizionario Biografico degli Italiani* (Roma: Istituto Enciclopedia Italiana Treccani, 2013): [https://www.treccani.it/enciclopedia/giovanni-bollea\\_\(Dizionario-Biografico\)/](https://www.treccani.it/enciclopedia/giovanni-bollea_(Dizionario-Biografico)/).

<sup>111</sup>Umberto De Giacomo to Ugo Cerletti, Lecce 5 December 1947, Letter, ES Section, Unit 4, Sapienza University, Rome.

Siena, reported to have tested twenty vials on an anxious-depressive woman and given other twenty vials to a colleague.<sup>112</sup> In 1948, the vials had reached different psychiatric centres throughout the Italian peninsula, including Turin, Milan, Brescia, Venice, Bologna, Siena, Perugia, and Brindisi.<sup>113</sup> In early July 1948, the psychiatrist Ferdinando Ugolotti, Director of the mental asylum in Pesaro, was regretfully informing Cerletti ‘they achieved nothing’ from injections with acroagonines on a manic-depressive patient, in contrast to successful results obtained with 3–4 ECT applications on the same patient.<sup>114</sup> In late September of the same year, Ettore Menichetti, at the Psychiatric Hospital in Perugia, achieved positive results in tests on three patients, but wished to take time to produce a proper report.<sup>115</sup> Only a few months before, in January 1948, a summary published in *The Lancet* might have put pressure on this research.<sup>116</sup> Arthur Spencer Paterson, who worked at the West London Hospital and was anxious to visit Cerletti in March,<sup>117</sup> organised the publication. This prestigious announcement of Cerletti practicing inoculations on humans – ‘in doing so he has opened new vistas of speculation’ – might also have stimulated the attention acroagonines received internationally (this is confirmed by the many letters Cerletti got on this matter from foreign colleagues in the years 1949–53<sup>118</sup>).

On 26–27 September 1950, the first *Congrès mondial de psychiatrie* in Paris, a cutting-edge venue organised by Jean Delay and Henri Ey at Sorbonne University, took place. The congress, the first after the war, gave birth to the World Psychiatry Association. In the fourth session chaired by the Brazilian psychiatrist Antonio Carlos Pacheco y Silva, Cerletti gave the first of three keynote speeches<sup>119</sup> and was then awarded an honorary degree by Sorbonne.<sup>120</sup> The following two speakers were the eminent shock therapists, Manfred Sakel and Ladislav Meduna. In another session, Cerletti presented also a black-and-white documentary edited with Longhi in collaboration with Istituto Nazionale Luce. The video, for which they were got a scientific prize in Rome,<sup>121</sup> showed the research on animals they conducted at the ES Center. The documentary, realized in two versions (1950, 1954), followed a tradition of scientific cinematography established at the beginning of the twentieth century in Italy and renovated after WWII thanks to investments from the CNR, the same research agency financing Cerletti’s experiments.<sup>122</sup> To produce it, Cerletti was given a sum of 800 000 Lire.<sup>123</sup> After a short theoretical introduction offered by Cerletti himself, the movie showed ECT administrations on nineteen vertebrates of different species in experimental settings (i.e. poikilotherms: carp, toad, frog, turtle, monitor lizard and boa; homeotherms: duck, swan, penguin, rabbit, porcupine, cat, dog, pig, sheep, mutton and monkey) and described their motor and behavioural reactions. The video was driven by Darwinian insight, that is, looking experimentally for the evolutionary roots of the mechanisms of action of electricity on the animal brain. Its goal was clearly to show Darwin’s terror-defence theory. The documentary concluded that ‘convul-

<sup>112</sup>Antonio D’Ormea to Ugo Cerletti, Siena 30 December 1947, Letter, Ugo Cerletti Collection, Unit ID 36465, KSHS Archives.

<sup>113</sup>Correspondence, Ugo Cerletti Collection, Unit ID 36463, Unit ID 36465, KSHS Archives.

<sup>114</sup>Ferdinando Ugolotti, 7 July 1948, Letter, ES Section, Unit 3, Sapienza University, Rome.

<sup>115</sup>Ettore Menichetti to Ugo Cerletti, 29 September 1948, Letter, Ugo Cerletti Collection, Unit ID 36465, KSHS Archives.

<sup>116</sup>‘Electroplexy explained?’, *op. cit.* (note 34).

<sup>117</sup>Arthur Spencer Paterson to Ugo Cerletti, London 10 February 1948, Letter, ES Section, Unit 8, Sapienza University, Rome.

A paper accompanying Paterson’s letter contains the pencil sketch of the hypophysis (Figure 3).

<sup>118</sup>These letters are now stored at the KSHS Archive and came from different world cities (i.e. Belgrade, Hamburg, Amsterdam, Budapest, New York, Philadelphia, Paris, London, Montpellier, Stockholm and Caracas). See Roberta Passione, ‘Non solo elettroshock: Ugo Cerletti e il rinnovamento della Psichiatria italiana’, in Marco Piccolino (ed.), *Neuroscienze Controverse: Da Aristotele Alla Moderna Scienza Del Linguaggio* (Torino: Bollati Boringhieri, 2008), 274.

<sup>119</sup>Three drafts of the speech Cerletti gave are in ES Section, Unit 3, Sapienza University, Rome.

<sup>120</sup>Ugo Cerletti’s Certificates, French Honors. Ugo Cerletti Collection, Unit ID 284156, KSHS Archives.

<sup>121</sup>Nuove ricerche e lavori relativi alla fisiologia dell’Elettroshock (1954–55), Typewritten Report of Activities of the ES Center, Unit 6, ES Section, Sapienza University, Rome.

<sup>122</sup>Passione, ‘Introduzione’, *Ugo Cerletti: Scritti*, *op. cit.* (note 6), 36–7.

<sup>123</sup>*Ibid.*

sion is not a brute, chaotic discharge caused by electricity, but the expression in various forms of a particular constellation of phenomena preformed in the brain, with an alarm-defence character'.<sup>124</sup>

A couple of months after the Paris Congress, Vincenzo Menichella at the Istituto dell'Assistenza all'Infanzia of the Province of Rome started treating twenty children (18–36 months), hospitalised in the luetic ward.<sup>125</sup> Ten were given shocked brain emulsions, ten were given non-shocked brain emulsions. It was reported that the emulsions protected all of them from an outbreak of paralytic polio in an adjacent ward. At a Congress in Taormina in 1951, Carmine d'Angelo reported to have injected eight elderly patients diagnosed with senile dementia at the Provincial Asylum in Rome.<sup>126</sup> Other forty-one patients, five of which affected by Parkinson's disease, were treated there by an intern from Paris, J. M. Dell, in 1952.<sup>127</sup> Cerletti was overly optimistic in interpreting the results.

Curiously enough, in 1953, Cerletti got his last chance with acroagonines, when his friend Pacheco y Silva decided to invest in Cerletti's acroagonines by involving a Brazilian company, Vincente Amato Sobriho s.a. in San Paolo. The admiration Pacheco y Silva had for Cerletti was profound, as he stated to the press.<sup>128</sup> The Hungarian psychiatrist Ladislav Meduna – inventor of the cardiazol shock therapy – who in the meantime had emigrated to Chicago and was close to Cerletti as well, tried to get some funding in the United States.<sup>129</sup> Phoenix physician Jacob Reichter and the Crease Clinic of Vancouver had invested in Cerletti's brain serum.<sup>130</sup> These investments, however, came late as companies in Cuba, Buenos Aires and Rio had already started acroagonine production without Cerletti's authorization.<sup>131</sup>

Unfortunate events for Ugo Cerletti, however, came in 1956. Both the Brazilian and USA trials on acroagonines proved discouraging. On 20 February of the same year, Cerletti's greatest supporter Guido Vernoni died.<sup>132</sup> In the absence of Vernoni, the ES Center could not survive. It was officially closed on 1 July 1957.<sup>133</sup> In the latter years, Cerletti had lost his academic influence, and precisely after 1952, when the newly appointed Clinic director Mario Gozzano had expelled Cerletti's close collaborator Vittorio Challiol,<sup>134</sup> who was acting director in the years 1949–51 and favoured Cerletti's activities at the Clinic. From that point, Mario Gozzano dismantled Cerletti's team, including Bini, Martinotti, and finally Longhi, by making strong, false and humiliating accusations to them – they had little scientific production, he unfairly reported in different occasions to the Faculty.<sup>135</sup> They were actually very prolific by assisting Cerletti on his research on the effects of ECT, while Gozzano intended to build his own team dedicated to EEG. In 1949, Cerletti had pointed out that 'during this last year alone, thirty-five works of my own team have been published or are in print'.<sup>136</sup> He had also somehow predicted the future of his team: 'If a professor, who has publicly declared himself opposed to the E.S. [electro-shock] in a congress, comes to Rome', he had said, alluding to Gozzano, then 'all this fervour of activity will be radically cut off'.<sup>137</sup> Forced to resign from his assistant position in 1952, Giovanni Martinotti requested to stay

<sup>124</sup>Ugo Cerletti and Lamberto Longhi, in collaboration with G. Martinotti and P. Bertolino, *Fisiologia Comparata dell'Elettroshock* (Roma: Consiglio Nazionale delle Ricerche, Istituto Nazionale Luce) transcription, in *Passione, Ugo Cerletti: Scritti*, *op. cit.* (note 6), 225–6, 226.

<sup>125</sup>Cerletti, 'Conclusioni sulle acroagonine', *op. cit.* (note 48), 196–7.

<sup>126</sup>*Ibid.*, 199–200.

<sup>127</sup>*Ibid.*, 205–7.

<sup>128</sup>'Muito ha que se vê e aprender na velha Europa', Newspaper article, clipping, undated. ES Section, Unit 5, Sapienza University, Rome.

<sup>129</sup>Passione, *Il Romanzo dell'Elettroshock*, *op. cit.* (note 12), 164. Ladislav Meduna to Ugo Cerletti, Letter, Chicago 15 July 1955, Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>130</sup>'Brain serum reported substitute for shock', *Phoenix Gazette*, 27 November 1953.

<sup>131</sup>Passione, 'Non solo elettroshock', *op. cit.* (note 118), 275.

<sup>132</sup>Guido Vernoni's Folder AS 670, Historical Archive, Sapienza University, Rome.

<sup>133</sup>Canali, 'Il Comitato Nazionale di Consulenza', *op. cit.* (note 6), 481.

<sup>134</sup>Vittorio Challiol's Folder AS 5176, Historical Archive, Sapienza University, Rome.

<sup>135</sup>Lucio Bini's Folder AS 5095, Vittorio Challiol's Folder AS 5175, Mario Gozzano's Folder AS 4977, and Giovanni Martinotti's Folder AS 5309, Historical Archive, Sapienza University, Rome.

<sup>136</sup>Cerletti, Letter to Gemelli, *op. cit.* (note 21).

<sup>137</sup>*Ibid.*

without a stipend.<sup>138</sup> Lucio Bini, who had been offered a leading position at the San Camillo Hospital in Rome, left the Sapienza Clinic on 1 November 1956, but continued to deliver some courses.<sup>139</sup> Despite their tensions, in 1955, Cerletti went to great lengths to support Bini's application to become director of the provincial asylum, the *Santa Maria Della Pietà* Hospital, a position he was never awarded.<sup>140</sup> Being fired just 11 days after the ES Center's cessation (12 July 1957), Lamberto Longhi started a legal battle lasting 4 years, until he was reintegrated in 1961.<sup>141</sup> Cerletti unsuccessfully recommended Longhi for a psychiatry chair position at the Catholic University in Milan,<sup>142</sup> and for another within the Vatican Congregation.<sup>143</sup> While Martinotti continued teaching at the *Santa Maria Della Pietà* Hospital,<sup>144</sup> Fiume was deemed eligible to lecture at Sapienza.<sup>145</sup>

Ferdinando Accornero, another intellectually active Cerletti's collaborator, decided to continue his position as an assistant at Sapienza, from which he retired in 1975.<sup>146</sup> Interestingly enough, Giovanni Bollea – who since 1956 had been dedicated exclusively to child disorders at a ward at the Roman Clinic<sup>147</sup> – was the only one to find favour with Cerletti's successor, Mario Gozzano, and was confirmed as a staff member at Sapienza, where a few years later he established a child neuropsychiatry institute.<sup>148</sup> Bollea was responsible for preserving Ugo Cerletti's miscellaneous records, including the 'ES Section', at Sapienza University in Rome.<sup>149</sup>

In March 1961, Gozzano defended himself by blaming Cerletti. He asserted that, in 1947, Cerletti should have located his CNR Center at the Clinic, instead of at the Provincial Hospital. 'I certainly do not think that this was the best way to collaborate with me',<sup>150</sup> Gozzano emphasised. Cerletti, however, had made this decision before Gozzano came to Rome. 'And here we come to the question of your assistants, whom I would have dismissed one by one', Gozzano continued. When he arrived in Rome, he stressed, he was told that Lucio Bini, like some others, had already applied for positions in other hospitals. He also mentioned that Bini thought Cerletti and Gozzano 'had plotted behind his back' to block his university career. As for Longhi, 'he made no objection to my proposal not to reconfirm him', Gozzano defended himself. 'Thanks to my praise', he even added, 'Longhi's appeal for a reintegration to Sapienza was accepted'. Gozzano also complained that Cerletti had convinced him to go to the Roman Clinic, where unfortunately, he had been welcomed by 'a hostile environment'.

There were other advances regarding acroagonine research in the late 1950s – early 1960s, such as the investments by the Max Planck Institute in Germany, and a trip Cerletti made to the USA Electroshock Research Association in 1959. Moreover, traces of the acroagonine theory – especially the idea of a sleep/

<sup>138</sup>Giovanni Martinotti's Folder AS 5309, Historical Archive, Sapienza University, Rome.

<sup>139</sup>Lucio Bini's Folder AS 5095, Historical Archive, Sapienza University, Rome.

<sup>140</sup>Correspondence and drafts, dated October 1955, are stored in a folder named 'Conc. Bini' [Concorso Bini]. Ugo Cerletti Collection, Unit ID 36468, KSHS Archives.

<sup>141</sup>Lamberto Longhi's Folder AS 5074, Historical Archive, Sapienza University, Rome.

<sup>142</sup>Dean Francesco Vito to Ugo Cerletti, Letter, 22 March 1960. Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>143</sup>Monsignor Dino Staffa to Ugo Cerletti, Letter, 9 May 1961. Ugo Cerletti (attributed to), Typewritten Letter with CV, undated. Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>144</sup>Giovanni Martinotti's Folder AS 5309, Historical Archive, Sapienza University, Rome.

<sup>145</sup>So called '*libera docenza*'. See Mario Gozzano, *Relazione*, 25 November 1965, Sebastiano Fiume's Folder AS 10025 Historical Archive, Sapienza University, Rome.

<sup>146</sup>Ferdinando Accornero's Folder AS 5197, Historical Archive, Sapienza University, Rome.

<sup>147</sup>Fiorani, 'Bollea, Giovanni', *op. cit.* (note 110). Giovanni Bollea remained devoted to his mentor Ugo Cerletti and preserved part of Ugo Cerletti's Miscellany and papers at the Sapienza Child Neuropsychiatry Institute in Rome, which he inaugurated in 1967.

<sup>148</sup>Giovanni Bollea's Folder A751, Personnel Archive, Sapienza University, Rome. He also wrote a publication with the new director: Mario Gozzano, and Giovanni Bollea, 'L'ospedale psichiatrico infantile', *Infanzia Anormale*, 25 (1958), 3–10.

<sup>149</sup>Giovanni Bollea to Etta Cerletti, Letter, Rome, 21 November 1963, Giovanni Bollea's Archive, Library for the History of Medicine, Sapienza University, Rome. Cecilia Campedelli, Conversation with the author, Livia Castelli and Luca Tonetti, online, Rome 18 May 2020.

<sup>150</sup>Mario Gozzano, Letter to Ugo Cerletti, 4 March 1961. Ugo Cerletti's various files, Ugo Cerletti Collection, Unit ID 36464, KSHS Archives.



wake regulation, explored by Alvas Garcia already in 1950<sup>151</sup> – resisted in Cerletti's latest publications.<sup>152</sup>

Yet the season of acroagones had ended by then. Cerletti had been left with a secluded office at the third floor of the Clinic and had gone back to exhausting research on endemic goiter with Lamberto Longhi,<sup>153</sup> his last scientific effort before passing away (25 July 1963).

### Acroagones in psychopharmacological and neuroendocrine research: the Cerletti–Delay competition

To explore the impact of acroagones on subsequent research, we need to go back to the 1940s. In April 1949, Cerletti's pupil Giovanni Bollea, who at the time was training in Paris at Georges Heuyer's lab,<sup>154</sup> informed his mentor of the events at a faculty meeting at the University of Sorbonne when discussing possible nominations for *honoris causa* degrees:

Heuyer was close to Delay and says to him: I would propose Cerletti if I did not know that there were misunderstandings (or something like that) between you and him. Delay replies: You are right and you were right to remind me. ... Then he stands up and proposes the name [Cerletti] himself.<sup>155</sup>

Accordingly, Cerletti was awarded at the *Congrès* in Paris a year later, but it is worth clarifying the nature of the aforementioned disagreements. In June 1947, during the speech held at the Superior Health Institute in Rome on early acroagone tests, Cerletti explicitly accused Jean Delay of plagiarism.<sup>156</sup> According to Cerletti, Delay publicly heralded the idea of the hypothalamic-diencephalic site of ECT action as his own, while Cerletti himself had formulated and analysed this idea, as part of his emerging acroagone theory, in his first 1940 monography on the electroshock, published in a local journal in Italian (*Rivista Sperimentale di Freniatria*).<sup>157</sup> Cerletti blamed the Italian language and the fact that only years later, due to the circumstances of the war, did the Americans become acquainted with his work. Cerletti remarked that, 'In 1946, we find it [the diencephalon hypothesis], largely paraphrased, in the II and III sections of Jean Delay's volume *L'Electrochoc and Psycho-physiologie* without the name of its author [Cerletti] being mentioned once. And in many publications of subsequent years by other authors, for example, in the book by Delmas-Marselet, we see it cited as the diencephalic theory of Delay'.<sup>158</sup> These accusations were repeated in several of Cerletti's handwritten notes.<sup>159</sup>

In a letter to his friend, the publisher Ulrico Hoepli, dated 24 April 1947, Cerletti confided that, 'In my leather bag, where I keep the urgent files, for months, there have been the drafts, now crumpled, of a lashing article against two French professors (Delay and Delmas–Marselet) who have appropriated my concepts'.<sup>160</sup> 'The French ... grab the intellectual priority of the Italians', he insisted. 'They have a good

<sup>151</sup>Cerletti, 'Conclusioni sulle acroagone', *op. cit.* (note 48), 195–196.

<sup>152</sup>Ugo Cerletti, Carmine D'Angelo, and Clara Fronticelli, 'Unterschiedliche Effekte von Hirnsuspensionen aus dem mit Elektroschock behandelten und dem normalen Gehirn', *Archiv für Psychiatrie und Zeitschrift f. d. ges. Neurologie* 199 (1959), 133–7; Ugo Cerletti, Paolo Cerletti, and Carmine D'Angelo, 'Potentiation of narcotic action by the brain treated with an electric shock', *Nature* 194 (1962), 582–3. In the 1962 article, the ES Center is referred to as 'National Research Council Unit for Studies on Electric Shock Physiopathology'.

<sup>153</sup>T. Besozzi, 'Una nuova grande avventura per Cerletti', *Il Corriere dell'Informazione*, 27 January 1956.

<sup>154</sup>Sirgiovanni, 'Electroconvulsive therapy applications on children in the 1940s', *op. cit.* (note 27).

<sup>155</sup>Giovanni Bollea to Ugo Cerletti, Paris, 29 April 1949, Ugo Cerletti Collection, Unit ID: 36470, KSHS Archives, Topeka, Kansas.

<sup>156</sup>Cerletti, 'Sostanze di estrema difesa', *op. cit.* (note 28).

<sup>157</sup>Cerletti, 'L'Elettroschock', *op. cit.* (note 47).

<sup>158</sup>Cerletti, 'Sostanze di estrema difesa', *op. cit.* (note 28).

<sup>159</sup>Ugo Cerletti (attributed to), Hand drafted Notes, undated, Ugo Cerletti Collection, Unit ID 36470, KSHS Archives. See also Envelope, Rivendicazioni su Delay e Delmas-M, Ugo Cerletti Collection, Unit ID 36463, KSHS Archives.

<sup>160</sup>Ugo Cerletti to Ulrico Hoepli, 24 April 1947, Box Books, Articles Misc. papers, Ugo Cerletti Collection, Unit ID 36455, KSHS Archives.

game because everyone reads French and no one Italian'.<sup>161</sup> Maybe this is why Lamberto Longhi defended his mentor in a report in French, arguing that Delay had started working on such topics only in 1943.<sup>162</sup> In 1942, Carlo Petrò at the University of Pavia was engaged in providing further evidence to Cerletti's diencephalic localization, who he referenced, particularly through identifying changes in basal metabolic rate in electro-shocked schizophrenic patients. This was another local publication in Italian, though.<sup>163</sup>

Notoriously, in 1952, Jean Delay made advancements that Ugo Cerletti, with acroagonines, could not. Delay presented seminal experimental work with Pierre Deniker at Saint-Anne's Hospital in Paris, presented in six renowned papers,<sup>164</sup> which hailed the introduction of the first effective neuroleptic, chlorpromazine (CPZ), to psychiatry. At the time, the tensions between Cerletti and Delay had already been solved.<sup>165</sup> They, then, will share the frustration of not getting a Nobel Prize for their respective psychiatric achievements, ECT and CPZ.<sup>166</sup>

Psychiatric application of this phenothiazine amine product, a synthetic antihistamine originally prepared as an insecticide by entomologists and chemists for the US Department of Agriculture, was the outcome of work started at the French company Rhône-Poulenc from fall 1950.<sup>167</sup> Ignoring previous null findings by American researchers,<sup>168</sup> which similarly sought to prove the antimalarial effects of this compound, chemically close to a synthetic antimalarial agent (i.e. methylene blue), Marc-Antoine Charpentier and collaborators at Rhône-Poulenc began testing it for malaria, though they ended up classifying it as a potentiator for general anaesthesia. Before Delay and Deniker, the navy surgeon Henri Laborit, during research on artificial hibernation, had tested it on a severely agitated manic patient aged 24, Jacques Lh., at the military hospital Val de Grâce in Paris. Laborit's patient received CPZ with ECT and two other drugs, an opiate (peditine) and a barbiturate (penotal).<sup>169</sup>

Notably, CPZ was found to work as antipsychotic medication. Yet, the psychiatric research on CPZ was greatly associated with ECT, even if ECT was (and still is) indicated for severe depression.<sup>170</sup> Cerletti celebrated these achievements, claiming that chlorpromazine and reserpine had 'revolutionised the life of psychiatric institutions'.<sup>171</sup> Before, he had been attracted by Arthur Sackler's work on histamine therapy for mental conditions, a psychiatrist who in 1949 had focused on cortisone and ACTH as well.<sup>172</sup>

<sup>161</sup> *Ibid.*

<sup>162</sup> Lamberto Longhi, La théorie diencephalique de l'électrochoc et les théories diencephaliques de la psychopathogénèse de la psychose maniac-dépressive et de la schizophrénie, Typewritten drafts, undated, Ugo Cerletti Collection, Unit ID 36463, KSHS Archives.

<sup>163</sup> Carlo Petrò, 'Sul comportamento del metabolismo basale nella schizofrenia e sul meccanismo d'azione dell'elettroshock', *Il Cervello*, 22, 5 (1942), 175–81. ES Section, Unit 2, Sapienza University, Rome.

<sup>164</sup> Thomas A. Ban, 'Fifty years chlorpromazine: a historical perspective', *Neuropsychiatric Disease and Treatment*, 3, 4 (2007), 495–500.

<sup>165</sup> *Passione, Il Romanzo dell'Elettroshock*, *op. cit.* (note 12), 127.

<sup>166</sup> Nils Hansson, et al., 'Babinski, Bektherev, Cerletti, Head, and Hitzig: European neurologists nominated for the Nobel Prize 1901–1950', *European Neurology* 83 (2020), 542–9; Healy, *Pioneers in Psychopharmacology*, *op. cit.* (note 3).

<sup>167</sup> Judith Swazey, *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation* (Cambridge, MA: MIT Press, 1974).

<sup>168</sup> Henry Gilman and David A. Shirley, 'Some derivatives of phenothiazine', *Journal of the American Chemical Society*, 66 (1944), 888.

<sup>169</sup> Francisco López-Muñoz, et al., 'History of the discovery and clinical introduction of chlorpromazine', *Annals of Clinical Psychiatry*, 17, 3 (2005), 113–35. For researches of ECT in connections with CPZ since 1952, see Judith Swazey, *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation*, *op. cit.* (note 167), 122.

<sup>170</sup> Antidepressants (i.e. iproniazid first, and imipramine after) came around 1957. See Walter A. Brown and Maria Rosdolsky, 'The clinical discovery of imipramine', *American Journal of Psychiatry* 172, 5 (2015), 426–9.

<sup>171</sup> Ugo Cerletti (attributed to), Symposium di farmacoterapia, Typewritten drafts, undated, Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>172</sup> Mortimer Sackler, Raymond Sackler, and Arthur Sackler, 'The technique of histamine biochemotherapy and suggestions for its use in psychiatry', *The Journal of Nervous and Mental Disease*, 113, 1 (1953), 40–51; Solomon H. Snyder, 'Arthur M. Sackler and science', *Proceedings of the National Academy of Sciences of the United States of America*, 98, 20 (2001), 10994–5.

In psychiatry, CPZ became popular for its secondary properties, as it affected ‘a high degree of ‘central’ [brain] activity regardless of antihistaminic activity’.<sup>173</sup> These central brain effects (sedative, analgesic, hypothermic) of a synthetic antihistamine – especially sedation, the most clinically significant – could have been confirmed in animal models (i.e. rats) in the fall of 1947. Curiously – and this catches our attention – it was the insight that CPZ affected the diencephalon that drove Jean Delay to test this compound in psychotic patients. In their early work, Delay and colleagues claimed explicitly they were looking for ‘treatments likely to act by mechanisms inverse to those caused by shock methods’, analogizing to the idea of an alarm reaction, and that they had been attracted by Laborit’s method of affecting the vegetative system.<sup>174</sup> Delay and Deniker’s novelty was that they ‘administered chlorpromazine alone, with no other drug in combination’, and in doing so, they proved it successful.<sup>175</sup> More importantly, the link between CPZ and the diencephalic model was offered by theories about the action mechanisms of ECT. These were proposed to be localised in the hypothalamus from the neurovegetative effects observed and measured in the post-shock phase,<sup>176</sup> a notion that Delay supported with the findings of his experimental work in 1943,<sup>177</sup> and that he had defended theoretically in his 1946 book.<sup>178</sup> Ten years later, the diencephalon would go on to gain attention in international psychiatry.<sup>179</sup>

Certain authors have claimed that ‘Cerletti’s effort was particularly interesting from a theoretical point of view because it was directly influenced by Delay’s writings on the diencephalon’.<sup>180</sup> This narrative, opposed by some Italian scholars as soon as the 1960s,<sup>181</sup> contrasts with the aforementioned details from Cerletti’s archival and bibliographic records. That, on the diencephalon theory, Cerletti preceded Delay by 6 years, but that the latter was ‘evidently unaware of Cerletti’s explanation’,<sup>182</sup> was instead the interpretation put forward by Paterson in *The Lancet* in his 1948 article.

We may doubt that Delay was oblivious to Cerletti’s theory – as in his 1946 book Delay actually referenced Cerletti’s 1940 work at one point, mentioning Cerletti’s association of electric epilepsy with a terror-defence reaction<sup>183</sup> – but at no point did he explicitly acknowledge Cerletti with regard to the diencephalic hypothesis, a core point of Delay’s book. On the flip side, Cerletti claimed that Delay was ‘perhaps the only one who has read it [Cerletti’s 1940 work] thoroughly’.<sup>184</sup>

There are many points of convergence between Cerletti and Delay’s theories on the diencephalon. Frequent overlaps of bibliographic sources may simply be a sign of the psychiatric knowledge of the time but the two also shared the association of the diencephalic effects of ECT with humoral and hormonal reactions,<sup>185</sup> along with a theory of consciousness.<sup>186</sup> As Cerletti noted:

<sup>173</sup>P. Koetschet, ‘Can it be said that chlorpromazine has specific properties’, *International Record of Medicine*, 168 (1955), 295–300: 298. See Swazey, *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation*, *op. cit.* (note 167).

<sup>174</sup>Jean Delay, Pierre Deniker, and J.M. Harl, ‘Traitement des états d’excitation et d’agitation par une méthode médicamenteuse dérivée de l’hibernothérapie’, *Annales Médico-Psychologiques*, 110, 22 (1952), 267–73.

<sup>175</sup>López-Muñoz, *et al.*, ‘History of the discovery and clinical introduction of chlorpromazine’, *op. cit.* (note 169), 118.

<sup>176</sup>Émilie Bovet, ‘Créer des “territoires de convergences”: le cas du diencephale’, *Les Cahiers du Centre Georges Canguilhem*, 7, 1 (2018), 81–96.

<sup>177</sup>Jean Delay, ‘Sur l’analogie des réactions biologiques consécutives à l’électrochoc et à la ventriculographie’, *Revue Neurologique*, 75, 160 (1943).

<sup>178</sup>Jean Delay, *L’électro-choc et la psycho-physiologie* (Paris: Masson & Cie, 1946).

<sup>179</sup>Emilio Trabucchi, ‘Symposium internazionale sul diencephalo, Milano 3–4–5 Maggio 1956’, *Annali Ravasini*, 10, 15 May 1956.

<sup>180</sup>Émilie Bovet, ‘Biography of a brain structure: studying the diencephalon as an epistemic object’, *op. cit.* (note 10), 129.

<sup>181</sup>C. Berlucchi, ‘Una grave perdita per la scienza italiana, Ugo Cerletti’, *La Rivista Scientifica*, 4, 11 (1964), 289–302.

<sup>182</sup>‘Electroplexy explained?’, *op. cit.* (note 34).

<sup>183</sup>Delay, *L’électro-choc et la psycho-physiologie*, *op. cit.* (note 178), 47.

<sup>184</sup>Ugo Cerletti to Belloni, Letter, 10 February 1947. Ugo Cerletti Collection, Unit ID 36464, KSHS Archives.

<sup>185</sup>Delay, *L’électro-choc et la psycho-physiologie*, *op. cit.* (note 178), Ch. 5.

<sup>186</sup>Delay, *L’électro-choc et la psycho-physiologie*, *op. cit.* (note 178), Part III.

1940 – ES is not an electrical treatment – elect[ricity] is only a stimulus – *it is a treatment of diencephalic stimulat.[ion] that takes place by means of the epileptic attack, especially by means of the humoral-hormonal discharge.*

Prove it! Doussinet and Jacob blood. *Blood is a too complex liquid, it summarizes too many metabolic processes, better to go to the source, the brain!*<sup>187</sup>

A neuroendocrine theory of mental conditions was not only the basis of Cerletti's acroagonine theory but also the reflection of an interest he maintained from his early writings on the goiter. It seems that Cerletti was captured by the idea of an endocrine disequilibrium at the origin of the epileptic seizure, as he collected some 1935 publications in Italian reporting experiments on epileptic dogs, particularly through ablation of the pancreas and thyroid.<sup>188</sup> Cerletti used to define acroagonines as 'hormonal-humoral biochemical reactions', produced by the diencephalic neurovegetative system defensively, to safeguard animal life.<sup>189</sup> Besides this, it should be remembered that already, in 1932, Cushing had hypothesised a role of the pituitary-adrenal axis in depression, and ACTH had been isolated in 1933, with Kendall Reichstein then isolating cortisol a few years later.<sup>190</sup> Yet, *Psychosomatic Medicine* and *The American Journal of Psychiatry*, respectively, would acknowledge the role of ACTH in psychiatry with two dedicated journal issues only in 1949 and 1950.<sup>191</sup> Cerletti was interested in psychic effects of ACTH and cortisone,<sup>192</sup> and in experiments testing their effects at low dosages on epileptic children.<sup>193</sup>

The idea of a humoral syndrome during ECT was said to have originated from blood research conducted before 1940 by Cerletti's assistants Castellucci and Felici, who had, respectively, determined increased glycaemia levels and haematological modifications after ECT-provoked seizures.<sup>194</sup> These reactions were considered by Cerletti to arise from the nervous system, rather than due to the convulsive hyperactivity of the muscles, for example, from 'exaggerated glucose combustion'. Cerletti noticed that Delay had advanced further 'interesting considerations' and findings, including those coming from EEG under ECT and direct diencephalic stimulation through pneumoencephalography, but he contested Delay's idea that this humoral syndrome was *also* partially a result of the action of the muscles.

As for endocrine thinking, it is true that Cerletti was connected to a milieu of the time, particularly a revived interest in endocrine psychiatry, including experiments such as those with adrenal cortex extracts on schizophrenics in the late 1930s or with desoxycorticosterone acetate on catatonic patients in early 1940s.<sup>195</sup> Yet, Cerletti anticipated the later findings of many others with speculations for which he received no credit.<sup>196</sup> For instance, in 1951, based on the effects of ECT on the adrenal cortex, Max

<sup>187</sup> Underlined in the text. Ugo Cerletti (attributed to), Hand-drafted notes. Ugo Cerletti Collection, Unit ID 36461, KSHS Archives. Cerletti was referring to Doussinet, Jacob, 'Importance du facteur humoral dans le mécanisme de l'action thérapeutique de l'électro-convulsion', *op. cit.* (note 68).

<sup>188</sup> Vito Longo, 'Epilessia sperimentale e ghiandole endocrine (note 1: Pancreas)', *Bollettino della Società medico-chirurgica di Catania*, 7, 7 (1935), 467–75; Vito Longo, 'Epilessia sperimentale e ghiandole endocrine (note 2: Tiroide)', *Bollettino della Società Medico-Chirurgica di Catania*, 3, 8, (1935), 506–8. ES Section, Unit 3, Sapienza University, Rome.

<sup>189</sup> Cerletti, 'Sostanze di estrema difesa', *op. cit.* (note 28), 146; Ugo Cerletti, 'Fisiologia comparata dell'elettroshock', in *Passione, Ugo Cerletti: Scritti*, *op. cit.* (note 6), 221.

<sup>190</sup> Harvey Cushing, 'The basophil adenom of the pituitary body and their clinical manifestations, pituitary basophilism', *Bulletin of the Johns Hopkins Hospital* (1932), L137–195.

<sup>191</sup> Émile Bovet, 'Créer des "territoires de convergences": le cas du diencéphale', *op. cit.* (note 176).

<sup>192</sup> Paul Gookler and Joseph Schein, 'Psychic effects of ACTH and cortisone', (1953), Abstract, *Harford Institute of Living*, 1, 22 (1954), 81; Howard Rome, 'Certain psychodynamic aspects of the role of cortisone and allied substances in the production of psychologic responses', (1953), Abstract, *Harford Institute of Living*, 1, 22 (1954), 82. Both abstracts were stored in ES Section, Unit 1, Sapienza University, Rome.

<sup>193</sup> Angelo Chieffi, 'Osservazioni su alcuni casi di epilessia dell'età infantile (trattati con ACTH e cortisone)', *Rivista di Clinica Pediatrica*, 17 (1954), 1–17. ES Section, Unit 2, Sapienza University, Rome.

<sup>194</sup> Ugo Cerletti (attributed to), Quelques données de l'électro-encéphalographie en rapports à l'E.C., Typewritten drafts, Ugo Cerletti Collection, Unit ID 36465, KSHS Archives.

<sup>195</sup> Edward Shorter and Max Fink, *Endocrine Psychiatry: Solving the Riddle of Melancholia*, *op. cit.* (note 9).

<sup>196</sup> *Ibid.* His name is not referenced in contemporary reconstructions.

Reiss, Robert Hemphill, and colleagues proposed that depressed patients should be administered ACTH to stimulate the adrenal cortex.<sup>197</sup>

In his 1940 speculations on acroagonines, Cerletti put forward an array of ideas that were developed years later, and some that are still debated nowadays.<sup>198</sup> The neuroendocrine theory of ECT, formulated by Max Fink and Jan-Otto Ottosson in the 1970s, followed descriptions by Bernard Carroll and Brian Davies of the dexamethasone suppression test, where dexamethasone suppressed ACTH and thus enabled an assessment of the levels of cortisol in the blood of depressed patients (so-called Cushing's disease).<sup>199</sup> According to its defenders, neuroendocrine theory is sustained by a series of neuroendocrine abnormalities (e.g. release of ACTH, cortisol, and prolactin in the blood after hypothalamic stimulation via ECT). The theory serves both to explain endogenous depression and ECT's action.<sup>200</sup> More importantly for the scope of this article, neuroendocrine theory was (and still is) 'a viable theory that sees seizures as changing brain and systemic endocrine relationships, like Cerletti but unrelated to his image'.<sup>201</sup>

### Final remarks

The goal of this contribution was to present Ugo Cerletti's audacious acroagonine research in a new, less-disqualifying light than before. The reconstruction offered herein was not intended to be exhaustive or conclusive though, and many questions remain for future historical investigations.

It was argued that with his research and theoretical insights, Cerletti paved the way for the development of psychopharmacology, whose explosion began after 1953, with the licencing of chlorpromazine on the market.<sup>202</sup> Looking beyond the diatribes between Cerletti and Delay on the paternity of the diencephalon hypothesis, this reconstruction emphasised that ECT, often seen as opposed to pharmacology, was a crucial step towards discovering psychotropic drugs. We must also take into account that Cerletti's hypothesis of psychoactive substances in the brain was conceived before the experimental confirmation of the neurotransmitters and the identification of the biogenic amines in the mid-1950s and that of *b*-endorphins in the 1970s, which have been shown to be involved in ECT-induced physiological effects.<sup>203</sup> Cerletti's claims were seen by his contemporaries to align with empirical findings that certain substances with the capacity for 'pharmacological action' on the vegetative neural system and on patients' hormonal states had been identified through ECT research on dysthymic patients, though this substance 'was not acetylcholine'.<sup>204</sup>

<sup>197</sup>Max Reiss, et al., 'Adrenocortical responsibility in relation to psychiatric illness and treatment with ACTH and ECT', *Journal of Clinical and Experimental Psychopathology*, 12, 3 (1951), 171–83.

<sup>198</sup>See Tom G. Bolwig, 'How does electroconvulsive therapy work? Theories on its mechanism', *Canadian Journal of Psychiatry*, 56 (2011), 13–8.

<sup>199</sup>Bernard J. Carroll, F.I.R. Martin and Brian Davies 'Resistance to suppression by dexamethasone of plasma 11-O.H.C.S. levels in severe depressive illness', *British Medical Journal*, 3 (1968), 285–7.

<sup>200</sup>Max Fink and Jan-Otto Ottosson, 'A theory of convulsive therapy in endogenous depression: significance of hypothalamic functions', *Psychiatry Research*, 2, 1 (1980), 49–61; Max Fink, 'Neuroendocrine predictors of electroconvulsive therapy outcome. Dexamethasone suppression test and prolactin', *Annals of the New York Academy of Sciences*, 462 (1986), 30–6; Roger F. Haskett, 'Electroconvulsive therapy's mechanism of action: neuroendocrine hypotheses', *The Journal of ECT*, 30, 2 (2014), 104–10.

<sup>201</sup>Max Fink, Email Correspondence with the author, 31 March 2021.

<sup>202</sup>Joel T. Braslow and Stephen R. Marder, 'History of psychopharmacology', *The Annual Review of Clinical Psychology* 15 (2019), 25–50.

<sup>203</sup>Francisco López-Muñoz and Cecilio Alamo, 'Historical evolution of the neurotransmission concept', *Journal of Neural Transmission*, 116 (2009), 515–33; Fernando Liggio, 'Le terapie bio-umoralì da induzione', in Antonino Iaria, Tommaso Losavio, and Pompeo Martelli (eds), *L'Ospedale S. Maria della Pietà di Roma, Dal Manicomio Provinciale alla Chiusura*, Vol. III (Bari: Edizioni Dedalo, 2003), 175–88: 187.

<sup>204</sup>Dino Bolsi, to Ugo Cerletti, Letter, Turin, 22 June 1948. Ugo Cerletti Collection, Unit ID 36465 KSHS Archive. The reference is to: C. Ajmone-Marsan and M.G. Fuortes, 'Electrographic study of the convulsant action of intravenously administered acetylcholine', *Electroencephalography and Clinical Neurophysiology*, 1, 3 (1949), 283–90. See also Mario

Cerletti's mistake was to have inferred the existence of acroagonines from the observed clinical effects without carrying out biochemical analyses.<sup>205</sup> The biochemistry of acroagonines remained his greatest concern,<sup>206</sup> and we may wonder whether this influenced his son Paolo's choice of profession. Paolo became a biochemist in 1959<sup>207</sup>; at the time, Ugo Cerletti was still 'waiting, with the friendly collaboration of American biochemists, to determine the chemical formula of the acroagonines'.<sup>208</sup> He never expressed 'any doubt about the existence of acroagonines'.<sup>209</sup>

Seven years before the discovery of chlorpromazine, Cerletti was asserting that 'it will be necessary, above all, to face [the problem of] the isolation of the active principles of acroagonines. I already said that'. 'For this enterprise', he claimed 'the biochemists are asking us for new and safe tests, but we have seen that the biological tests available are slow and complicated. When the biochemists have given us the chemical formula or formulas of the acroagonines, they will perhaps be able to reproduce them by synthesis, and then we will not only have freed man from E.S. [electroshock], but also the animals'.<sup>210</sup> 'For now, therefore', he insisted, 'we cannot answer the question about *what these acroagonines are*; but neither do we intend to venture into reasoning about their mode, or better their *modes*, of action in the various tests made on man and animals'. Nonetheless, as the following years would prove, he was wrong in his conclusions that, 'We do not need to hurry; we must be satisfied, as we have been, with completely generic explanations'.<sup>211</sup>

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<sup>205</sup>Canali, 'Il Comitato Nazionale di Consulenza', *op. cit.* (note 6).

<sup>206</sup>Ugo Cerletti (attributed to), Reponse des rapporteurs, undated. Ugo Cerletti's various files, Congr. Parigi 1950, Ugo Cerletti Collection, Unit ID 36464, KSHS Archives. Ugo Cerletti, Carmine D'Angelo, Test rapido e sicuro per determinare le acroagonine, Typewritten notes, undated, Ugo Cerletti Collection, Unit ID 36469, KSHS Archives.

<sup>207</sup>Paolo Cerletti's Folder AS 7192, Historical Archive, Sapienza University, Rome.

<sup>208</sup>Ugo Cerletti, Hand-drafted notes, (datable) 1959, Ugo Cerletti Collection, Unit ID 36461, KSHS Archives.

<sup>209</sup>Ugo Cerletti and Carmine D'Angelo, Test rapido per differenziare il cervello sottoposto a Elettroshock dal cervello shockato, Riassunto della comunicazione al Congresso Internazionale di Psichiatria, Zürich 3–6 October 1957. Ugo Cerletti Collection, Unit ID 36466, KSHS Archives.

<sup>210</sup>Cerletti, 'Conclusioni sulle acroagonine', *op. cit.* (note 48), 208.

<sup>211</sup>*Ibid.*

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