

## THE ACETYLCHOLINE THERAPY IN THE TREATMENT OF SCHIZOPHRENIA – THE EXPERIENCE OF MARIO FIAMBERTI IN THE HOSPITAL OF VARESE (1937)

### TERAPIJA ACETILHOLINOM U LIJEČENJU SHIZOFRENIJE – ISKUSTVO MARIJA FIAMBERTIJA U BOLNICI VARESE (1937.)

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#### SUMMARY

*In the first half of the 20th century, in most European countries, it was thought that cholinesterase and other drugs that counteract acetylcholine should reduce the manifestations of schizophrenia. In 1937, Fiamberti (1894–1970) introduced the transorbital method of lobotomy which established the use of acetylcholine shock treatment for curing the disturbances of schizophrenia.*

*Accepting the idea that the psychic alterations of schizophrenia were caused by a pathological interruption of nerve conduction at a presumably cortical level, Fiamberti thought he could apply this to the clinical field using the properties of acetylcholine, an acetic ester of choline.*

*Here, we examined, in detail, the contribution of Mario Fiamberti to acetylcholine therapy.*

**Keywords:** *acetylcholine therapy, Fiamberti method, acetylcholine shock, schizophrenia and interpretative hypothesis, acetylcholine deficiency, schizophrenia*

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Mario Fiamberti (10 September 1894-1970) was an Italian psychiatrist who achieved his greatest notoriety and a strong influence on psychiatry of his epoch. After graduating from the University of Turin, he devoted himself to the study of nervous and mental illnesses and to the career of asylum doctor.

He worked in the psychiatric hospitals of Brescia, Sondrio, and Vercelli, and became the Director of the Psychiatric Hospital of Varese since its opening in 1939.

In 1937, he performed a transorbital lobotomy, by accessing the frontal lobe of the brain through the orbits. The technique remained rarely practiced until his reports were discovered by his contemporary, the American neurologist Walter Freeman, who improved the surgical technique, initially by using ice picks (hence the name “ice pick lobotomy”) and later employing more refined equipment [1,2,3,4].

In 1935, Fiamberti provoked convulsions in experimental animals by the administration of injections of acetylcholine, a substance capable of inducing crisis, and in 1937 proposed this special method of shock for treating psychotic patients.

In neurophysiology during 1900-1950, neurohumoral knowledge of the time and the development of the study of chemical mediation at the level of brain synapses led to the formulation of many hypotheses with a superficial view of physiological and biological data [5].

Still today, schizophrenia represents a chronic psychotic disorder that continues to be controversial.

In the uncertainty of the moment, the discussion on the relationship between epilepsy and schizophrenia [6] began at the same time the psychiatric clinic scene was establishing Cardiazol, which had been introduced by Joseph Ladislav Meduna (1896-1964) for epileptogenic activity in 1935 [6,7,8,9,10,11].

Originating from the idea that psychic alterations of schizophrenia were due to a pathological interruption of nerve conduction at cortical level, Fiamberti was convinced that he could act in the clinical field using the properties of acetylcholine, an acetic ester of choline.

Fiamberti believed that acetylcholine had a fundamental role and effectiveness in neural transcription. The injection of large quantities of this substance was able to, in the opinion of the Italian psychiatrist, stimulate and

regulate the physiological mechanism to promote and determine the diffusion of acetylcholine in the nerve centers.

The proposal for the treatment of schizophrenia with acetylcholine was therefore a part of the general confident adherence to the shock therapies. That is, the theoretical assumption continued to be that of Meduna on the antagonism between convulsions and schizophrenia.

The search for new substances (ammonium chloride according to the proposal of A. Bertolani, adrenaline according to that of V. Cacciapuoti, and acetylcholine according to that of Fiamberti) or other alternative methods for the convulsive therapy capable of inducing a state of shock were however stimulated by the attempt to limit adverse effects.

Fiamberti favored the use of acetylcholine in shock therapy because of its theoretic implications, as well as its practical convenience and safety. Furthermore, Fiamberti did not report side effects.

As therapy of psychosis, the use of acetylcholine would have determined the clinical improvement of the patient.

The biological activity of acetylcholine, synthesized by Nothnagel in 1894 and isolated in the rye by Ewins in 1914, was calculated to be enormously superior to that of choline.

Fiamberti presented his proposal, entitled *Epileptic accesses caused by the introduction of substances vasodilatory under occipital*, to the 21<sup>st</sup> National Congress of the Italian Psychiatric Society in Naples. He demonstrated that the introduction of an acetylcholine in an aqueous solution via the occipital route caused convulsive fits of epileptic type and therefore the substance seemed to be able to replace cardiazol. From these experiences, an attempt was born to introduce this therapeutic technique in a psychiatric clinic.

On November 14<sup>th</sup>, 1937, at the convention on modern therapy for schizophrenia in Milan, the research of Fiamberti had the explicit title *Proposal of a new method (vascular shock) of provocation of convulsive accesses for therapeutic purposes with the use, for intravenous route, of acetylcholine*. The first results that were obtained in the clinic, he considered positive, so he could make them public knowledge.

In February 1940, at a meeting of neurologists in Bologna, the psychiatrist revealed the therapeutic results obtained from 120 schizophrenic patients, who had been diagnosed in a less than a year, boasting that 78% of clinical remissions were followed by a hospital discharge.

The first hypotheses of Fiamberti had focused on the action of the substance on circulatory changes, so obvious to obtain the definition of “vascular storm” [12]. We must note that Fiamberti considered his method of shock to be elective for schizophrenia, while he considered it improper in the dysthymic or confusional syndromes. We must remember that for certain manifestations of psychiatric diseases it must have been difficult to diagnose, with confidence, a manic depressive psychosis with hope of remission, and the “precocious dementia” in front of which one remained therapeutically in a negative position. For maniacal-depressive psychosis, Fiamberti relied on high-dose intravenous calcium and autohemotherapy, but in schizophrenia the approach was more difficult: the treatment of sulphur-therapy, protein-therapy, and the novelty of shock with insulin, and cardiazol were now added to acetylcholine.

There was still no revolutionary proposal of electric shock treatment by Ugo Cerletti.

The incomprehensibility of the dissociative phenomenon stimulated audacious interpretations and gave voice to the hypothesis of a dysfunction of the inter-neuronal transmission due to the lack of a chemical-humoral mediator, the fundamental pathogenetic element. At the beginning of the last century, thanks to the confidence in neuropathology, it was possible to penetrate the etiological mechanisms of mental illnesses, the biological, bio-electrical and clinical modifications in the main pathologies that had caused hospitalization in psychiatric institutions.

Fiamberti adhered unreservedly to the “*pathophysiological interpretation, which I seem reasonable to propose to the attention of scholars, of ‘mental dissociation’ considered primitive and fundamental symptom of early dementia (Bleuler’s school) as an effect of a disturbed or non-transmission of nervous current at the level of interneuronic synapses, depending on a deficiency of acetylcholine*” [13].

From this perspective, it was not difficult for Fiamberti to believe that with acetylcholine the synaptic nerve impulse could be modified, and act on dissociative symptoms. He theorized the mechanisms of action of acetylcholine therapy by inserting his hypothesis into the visions of a biological pathogenesis of schizophrenia. Understanding that the alterations of schizophrenia derived from a pathological interruption of nerve conduction at the cortical level, it seemed that acetylcholine determined an improvement in dissociative symptomatology through the restoration of altered neuronal relationships at the level of the central synapses with a psychic function [14]. It

was the neurohumoral theory of mental dissociation of psychiatric research and the clinic of nervous and mental diseases who expressed an almost unanimous adherence to these theoretical hypotheses. Fiamberti recorded his observations in a 450 paged manuscript, with which he obtained the 24<sup>th</sup> National Psychiatry Congress Award in Brazil. The injection of acetylcholine directly into the brain always produced a convulsive effect, however, it did not seem that the same effect could be obtained with intravenous administration. All the authors agreed on this difference, furthermore, some experiments linked the effects on the nervous substance to the circulatory changes most certainly induced by the substance. Fiamberti's proposal did not limit to consider the convulsive effect of acetylcholine efficacy. It reflected on the question whether it was *"really necessary to get to the convulsive crisis or it was not enough to provoke a lighter one with diminished doses that, without giving convulsions, could be as effective as the therapeutic effects"* [15]. He wanted to release his method from the necessity of the convulsive effect to channel it into the medical therapy on the basis of physiopathological concepts. In his treatment, he studied the blood chemistry parameters and the liquor before and after therapy, he studied the bioelectrical alterations of the brain, but the complexity of the mechanism of action was not revealed. An "ideal crisis" was the one accompanied by a loss of consciousness with impressive manifestations of vegetative and vascular order. In adults it was reached with the standard dose of 0.50 gram (0.40 for the lyophilized product), but it could also be experienced in larger doses. In the standard set of 1943, the cure consisted of 100 injections, one a day with a day of rest each week, similar to the Sakel scheme, but prolonged or continued treatments were also practicable. Intravenous injection with a large-caliber needle was to be carried out very quickly: in 3-5 seconds, the patient felt a sense of suffocation and turned from the supine position. After this first prodromal phase, the patient became exhausted by a long expiratory phase in the form of frequent seizures of dry coughing, while the conscience became numb; in 15-20 seconds, shock with loss of consciousness. With or without a prolonged inhalation, the patient became rigid in a generalized tonic crisis, with hyperextension of the limbs (almost to configure a fleeting phase of opisthotonus), rotation of the head, and the ocular globes, with intense pallor, mydriasis and rigidity to the luminous stimulus, and wrist movement similar to the effect of cardiac arrest. After another 10-15 seconds the fourth phase began, awakening: brief and disordered clonic shocks and imposing neurovegetative manifestations; from pallor to reddening of the face, followed by sweating, tearing,

salivating; once the clonic shocks are over, breathing and a steady pulse are resumed; the recovery of consciousness was “lightning” and characterized by hyperlucidity.

In all, 20-30 seconds had only passed, and the patient left the bed in a few minutes. This was a quick and simple method. It required the assistance of a single nurse in the face of the electroshock ceremony with several other figures on the scene. Fiamberti could proudly boast of it, being the most innocuous of methods, despite the dramatic nature of some manifestations and cardiac arrest. There were no accidents, bone fractures, or late amnesia, etc. in 300,000 applications at the hospital of Varese. For prudence, it was better to keep vials of atropine sulphate ready at 1 per thousand in the event of prolonged clinical effects. A summary of Fiamberti's thoughts can be found in the study of a student of his, Edoardo Balduzzi, who published a book on shock therapies in 1962, dedicating about thirty pages to acetylcholine shock. In this text, the comparison with the other biological therapies of the time is presented [16]. Furthermore, a critical discussion of this treatment modality and of other shock-therapy methods with evaluating the advantages and disadvantages is presented in the text of Liberati [17]. Balduzzi observed that acetylcholine therapy had gained more confidence abroad than in Italy, with reports of scientific consensus from Norway, Denmark, North and South America, etc. and this perhaps marked a mature trait of appreciable caution among the Italian psychiatrists of the time. A demonstration of a direct cerebral effect was given by performing experiments on animals and Giorgio Cenacchi, another student of Fiamberti, in 1953 tested the effect on a man in Varese with double electroencephalographic and electrocardiographic recordings. The strong doses of acetylcholine were able to reach the encephalic circulation despite the cardiac arrest caused by excessive vagal stimulation. In the middle of the last century in psychiatric therapy, electric shock had dominantly imposed itself on other techniques, but Fiamberti still did not break away from the confident adherence to his treatment. From the hospital of Varese, they proposed to the community of psychiatrists apparently satisfactory results that seemed to confirm the validity of the bio-humoral theory of mental dissociation and of acetylcholine treatment.

The technique was considered to be good in pure and recent dissociative syndromes, but mostly it was considered effective only if completed on each subject with at least 100 doses: *“Who today, in front of a schizophrenic, especially early, does not apply the acetylcholine therapy (also associating, if he believes in Sakel's therapy), in my opinion, he lacks a precise duty as a doctor, because he*

deprives his patient of the possibility of obtaining a result that the facts show has often been achieved even when the other therapies, including that of Sakel, had failed” [15]. Today, on the pages of the volume from 1946 and many other works dedicated to acetylcholine in previous years, and in the following, we read the long scientific explanations at the intersection of physiology and biochemistry that affect our sensitivity through a series of photographs showing the dramatic visible effects of therapy on patients (Figure 1). “Purely for the purpose of documentary aid, it may be of some interest to submit photographic images of some patients performed on at the time they enter the hospital and when recovered, mostly after discharge. I know well how little importance this documentation can have on the demonstration side; in fact, the photographic technique can make the subjects appear differently, regardless of their attitude referable to particular psychic conditions. However, psychiatrists may need to consider certain elements that are relative to



Figure 1. Photo showing the dramatic effects of therapy on patients (From Fiamberti AM. L'acetilcolina nelle sindromi schizofreniche. Interpretazione patogenetica della dissociazione mentale e sua applicazione terapeutica. Firenze: Niccolai; 1946).

the method, in particularly photographic examination, used when evaluating expressions and physiognomic attitudes with their practiced eye” [18]. It is necessary to report the testimony of some elderly nurses who remembered that, precisely because of the hinduostatic suffering and contortions (see the photography), the doctors in charge of administering acetylcholine often disregarded the instructions of the director of the asylum. Certainly, the ingenuity of the volume is surprising and together with the long casuistic and statistical tables, they proposed to use different photographic portraits of patients at the hospital admission and also after some time of care (Figure 2) [18]. Above all, looking at these photographs, we can better understand the testimonies of the nurses who were working in the Hospital of Fiamberti at that time and remembered that, precisely because of the obvious cenestopathic suffering and the patient contortions, the doctors sometimes disregarded the director's prescription in order to administer acetylcholine.



Foto A. Foto B.  
V.... Pietro — Caso n. 39 della statistica generale.



Foto A. Foto B.  
B.... Elide — Caso n. 44 della statistica generale.

Figure 2. Photos of patients at the hospital admission and after the cure  
(From Fiamberti AM. *L'acetilcolina nelle sindromi schizofreniche. Interpretazione patogenetica della dissociazione mentale e sua applicazione terapeutica.* Firenze: Niccolai; 1946).

The signs left on the bodies and the lives of the people portrayed, like those of the many who have undergone coercive treatments, solicit considerations regarding the ethical profiles of these practices, their impact on the

therapeutic relationship and, also, on the perception of psychiatry dominant orientation at the time.

Forty years after the introduction of the Law 180 in 1978, there have been many changes in ethics and rights, particularly of those vulnerable people, who have expressed themselves in psychiatric clinical practice [19,20].

The Fiamberti's method, after a brief period of diffusion and application in the 1950s, quickly set for the fragility of its theoretical basis and for the lack of knowledge about all the specific and qualifying symptoms of schizophrenia (including its subtypes). Thus, it now belongs only to the history of medicine and, in particular, to the non-linear and complex pathway of psychiatry [21,22,23].

The treatment of Fiamberti, though dated and abandoned, retains interest not only as a purely historical reconstruction in the treatment of schizophrenia, but also for the insights that it had.

The recent scientific research has now proven that the basis of some psychiatric disorders is – including that of schizophrenia – the absence of an appropriate development of neurological connections and, consequently, the neurological disconnection [24,25,26].

The latest scientific researches, together with the use of the new antipsychotic drugs, re-propose the relationship between dopamine and cognitive dysfunction in schizophrenia.

Although the modulation of dopamine neurotransmission has been a dominant therapeutic approach, the results of both clinical and preclinical researches suggest that the dysregulation of other neurotransmitter systems, including acetylcholine, contributes to the pathophysiology of schizophrenia [27,28].

Recent research identifies the possibility that kynurenic acid is able to decrease the activity of acetylcholine and glutamate in brain activity.

The historical reconstruction of this treatment allows the recognition of the work of Fiamberti who, despite the limits of scientific and pharmacological knowledge of that time, has identified in the acetylcholine a substance that plays a significant role in the antagonism of schizophrenia.

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## SAŽETAK

*U prvoj polovici 20. stoljeća u većini se europskih zemalja smatralo da bi kolinesteraza i drugi lijekovi koji djeluju protiv acetilkolina trebali smanjiti manifestacije shizofrenije. Godine 1937. Mario Fiamberti (1894. – 1970.) uveo je transorbitalnu metodu lobotomije koja je utvrdila upotrebu acetilkolinske šok-terapije u liječenju poremećaja shizofrenije.*

*Prihvatajući ideju da su psihičke promjene shizofrenije uzrokovane patološkim prekidom živčane provodljivosti na vjerojatno kortikalnoj razini, Fiamberti je mislio da to može primijeniti na kliničkom polju koristeći svojstva acetilkolina, acetilnog ester kolina.*

*U istraživanju je detaljno ispitan doprinos Marija Fiambertija u terapiji acetilkolinom.*

**Ključne riječi:** acetilkolin terapija; Fiambertijeva metoda; acetilkolinski šok; shizofrenija i interpretativna hipoteza; nedostatak acetilkolina; shizofrenija