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Review

Giuseppe Moruzzi: A tribute to a "formidable" scientist and a "formidable" man

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ABSTRACT

Giuseppe Moruzzi was born one century ago; he was an outstanding Italian neurophysiologist, who was particularly famous for his contributions to the study of the mechanisms underlying the control of the sleep–waking cycle in mammals. In 1990, Rita Levi-Montalcini, Moruzzi's great friend and admirer, used the occasion of an invitation by the University of Parma, where Moruzzi graduated in medicine in 1933, to celebrate Moruzzi's scientific achievements. She wished to pay a tribute to Moruzzi's human and ethical qualities by portraying him as a "perfect model" for the young generation wishing to pursue scientific research. The transcription of "Rita's" tribute to Moruzzi links two of the greatest figures of Italian neuroscience and also provides a lively account of how the personal histories of two promising young scientists intertwined with the great and tragic events of world history in the past century.

Contents

It is with gratitude and emotion that I thank you for this extraordinary welcome, and for the generous words given by the Rector of the University and by the Dean of the Faculty of Sciences.[1] I wish to make it clear that I consider all of this is not due to me personally, but to the person that I have come here to honour today. His name is Giuseppe Moruzzi, a son of this land, a student of

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[1] This is a transcription, revised by the author, of the commemoration to Moruzzi by Rita Levi-Montalcini held at the University of Parma on March 20th 1990. The occasion of the invitation to Rita Levi-Montalcini by the University of Parma was a prize awarded to her by the municipality of Noceto, near Parma, where the family house of Moruzzi is situated in the locality of Bombodolo, an old mansion where he spent the summer periods since his childhood. Shortly before Levi-Montalcini's speech there had been the addresses of the Rector and of the Dean of the Faculty of Sciences praising the importance of her research, and of the scientific school in which she had received her training with Giuseppe Levi. The conference was attended by members of Moruzzi family and particularly by his wife Maria Vittoria Venturini-Moruzzi. The transcription and translation of Levi-Montalcini's words have been made in a way which attempts to maintain, at least in part, the oral character of the speech. A partial transcription of the same conference has been published in a recent volume which also includes Moruzzi's *Recollections* (Meulders et al., 2010).

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Fig. 1 – Pictures of Giuseppe Moruzzi and Rita Levi-Montalcini about the time of their first meeting. (© Giovanni and Paolo Moruzzi and Rita Levi-Montalcini).

this University, recognised not only in our country but throughout the world. Therefore what I am going to tell you and the honour that you bestow on me, is a tribute to the great neurophysiologist Giuseppe Moruzzi who unfortunately passed away four years ago. The tributes should be paid to him rather than to me — for what his entire life has been, for what he has done, which is much greater than what has undeservedly been acknowledged to me. Honours are, however, of no value for people of such stature as Giuseppe Moruzzi. He gave them no importance, and honestly I must say that I also give no importance to them. We shared the passion for research, and – I would say – a total honesty in carrying it out, along with the enthusiasm and the pleasure for what we have achieved.

Fig. 2 – Giuseppe Moruzzi, walking in Copenhagen in 1939, when he was attending the International Congress of Neurology in which he first met Levi-Montalcini, while the threat of the Second World War was darkening the skies of Europe. (© Giovanni and Paolo Moruzzi).

I will begin by remembering how we met, and what was the initial path we took together, even though eventually we went along different routes. We first met at a conference in Copenhagen[2] on a tragically historic day (see Figs. 1 and 2): it was the first of September 1939, the day of the invasion of Danzig. Moruzzi was just one year younger than me, he was much more handsome and attractive, and I was impressed by the fame he had earned at only 29 years of age. I was a shy young girl who had recently graduated and I was perfectly unknown to him. For racial reasons[3] I had been expelled, or – at least – obliged to leave my country and to take refuge in Belgium where I was offered work. On the day of our chance encounter in Copenhagen, the newspaper headlines were announcing the invasion of Danzig, which meant the beginning of war. We spent all day together, he had not yet met the companion of his life, Maria Vittoria. He, like myself, was in a state of despair because of the alarming impending events and

[2] The conference was the "III Internationale Neurolog-Kongress" held in Copenhagen from 21 to 25 August 1939. Moruzzi presented a communication based on his work with Adrian. (Adrian and Moruzzi, 1939a).

[3] In 1938 the Fascist Government of Italy started adopting, on the model of Nazi Germany, the so-called "racial laws", mainly aimed against Jews, which discriminated between people on the basis of a series of different criteria (Vittorio Emanuele et al., 1938, see Troiani and Manni, 2007). The declared purpose of these laws, based on a series of pseudoscientific assumptions, was to preserve the purity of the "Italian race". Among other things, the discriminated people were obliged to leave their positions as public officers. This also applied to university professors who lost their teaching positions and also any other academic and honorary titles. Unfortunately, ten Italian scientists signed the so called "Manifesto della Razza", a racist text, first published in a newspaper (Giornale d'Italia) on July 15, 1938, which prepared the grounds for the racial laws. This "list of shame" included, Lino Businco, a pathologist, Lidio Cipriani, an anthropologist, Arturo Donaggio, a neuropsychiatrist, Leone Franzi, a paediatrician, Guido Landra, an anthropologist, Nicola Pende, a clinician, Marcello Ricci, a zoologist, Franco Savorgnan, a statistician, Sabato Visco, a physiologist, and Edoardo Zavattari, a zoologist. As a consequence of the racial laws the situation of Jewish people in Italy became progressively worse resulting in persecutions and deportations. Many Jews, including Rita Levi-Montalcini and her teacher Giuseppe Levi (professor of anatomy in Turin) were evicted. Both fled to Belgium, Levi-Montalcini to Brussels and Levi to Liege. A reference to the poor conditions of Jewish people in Italy as a consequence of the racial laws is present in many of Levi-Montalcini's autobiographic writings (see particularly of Levi-Montalcini, 1996; Brizzi and Rita Levi-Montalcini, 2002). Among those who incurred the persecution, but did not leave the country, was Tullio Levi-Civita, one of the greatest mathematicians of his period. Another great mathematician of Jewish descent who did not leave Italy was Vito Volterra. He had already been evicted from his academic positions and public functions because of his refusal in 1930 to swear his fidelity to Fascism. To him Levi-Montalcini has dedicated a chapter of a book written in 1996. Like many members of his family, Moruzzi, while not Jewish, was strongly opposed to fascism. He deplored the lack of freedom in Italy during the Fascist period which eventually resulted in his prosecution by the secret police of the Fascist regime. In a letter written to the family from Copenhagen, on August 21, 1939 (i.e. during the period of his first meeting with Levi-Montalcini), he deprecated the communication presented to the congress by Arturo Donaggio, one of signatories of the "Manifesto della razza" (see Cosmacini, 1992).

Fig. 3 – Moruzzi and his wife, Maria Vittoria Venturini (1918–2006) in 1944, three years after their marriage. (© Giovanni and Paolo Moruzzi).

I was struck by the serious way in which this young man faced them. Leaving aside my critical situation, the whole world was then in danger. All day along, until late evening, we discussed what could be done. Eventually, every one of us returned to their countries. Moruzzi did not return directly to Italy but travelled by train through Germany. At that time he was working in Cambridge with Lord Adrian; the importance of their studies was already known, as I will indicate later. I went to Belgium, and from Belgium I came back to Italy when the war was nearing, and then we all know what happened. By a miracle both of us survived and we were destined to meet each other ten years later.

The circumstances in which we met again, perhaps better remembered by Maria Vittoria, who was then Moruzzi's wife (Fig. 3), were very different from the sinister and menacing atmosphere of 1939. The year of our second meeting was 1949 and the city was Chicago, where he had been working since 1948 at Northwestern University along with the great neurophysiologist Horace Magoun. In 1947 I had been invited to work at Washington University in St Louis and had the occasion to go to Chicago (Fig. 4) for a conference. I will never forget this second meeting with Moruzzi. I had learned about the formidable development of his research, and all afternoon I attended one of the presentations on the famous discoveries concerning the *arousal system*, the *ascending reticular system* (Moruzzi and Magoun, 1949: Fig. 5). I remember that we spoke about it, and together we reminisced about the times past. And from then on his research continued in a formidable way, as I will soon recount. Eventually both of us came back to Italy, Moruzzi almost immediately to Pisa, where he set up a laboratory that remains renowned nationally and internationally to this day (Fig. 6). I remained in the United States until 1961, when I re-established the contacts with Italy, but I settled down here only after 1979, by directing a research laboratory. In those years, after that first period, our meetings were very frequent. But I will recall an anecdote that seems amusing as seen from a distance of several years.

After the first meeting with Giuseppe Moruzzi, then young but already well known, I said to the famous Giuseppe Levi, a wonderful person but a singular character (see Fig. 7): "I met a young man who will make history in Italy". He looked at me and said: "Who is that?" I said: "Giuseppe Moruzzi is the name". With a rather mischievous air, he said: "Tell me, perchance have you become infatuated with this young man?" I said: "No, Professor, I am not infatuated, I recognise merit in men and women alike, you will hear of him". A few months later, after meeting Moruzzi, Levi said to me: "You know, he is a really formidable young man". I said: "Professor, did you perchance become infatuated with this young man?" He said: "You are a pretty insolent person". I said: "You made that accusation to me, and even if it was not an accusation, you did not interpret the admiration I have for Moruzzi correctly. I have the right to ask you how you have come to admire him as well". This indicates how this young person had struck me, not only in the sense… (we belonged to a different sex, there could be that…) … no, truly I had recognised in him a person of exceptional quality, from the scientific point of view and also from the human point of view.

From then almost to the end of his life, except in the last months when I no longer had the opportunity to see him, we repeatedly exchanged information about our work, and we always enjoyed the pleasure of meeting each other. Every time I met Moruzzi he was ever the young Moruzzi I had known, full of vitality. Even though at the end he suffered from a serious disease, nothing had changed with him.[4] The depth of his thinking, his scientific insight, his creative capacity, and what

[4] During the last years of his life Moruzzi suffered of a progressive form of Parkinson's disease which severely affected his motor abilities.

GENETIC NEUROLOGY

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Fig. 4 – Left: Rita Levi-Montalcini at the time of her second meeting with Giuseppe Moruzzi, when she learned about his experiments on the ascending reticular system. The occasion of the photo was a developmental neurobiology meeting held in Chicago from 21 to 25 March 1949. Many of those in this photograph are important scientists who made significant contributions to the progress of the neurosciences. In the second row, just behind Rita Levi-Montalcini, there are, from left to right: Ralph Gerard (one of the first to devise microelectrodes for electrophysiological recordings), Holger Hyden (the discoverer of the S-100 protein), Paul Weiss (the organiser of the meeting and one of the founders of neuroembryology), Francis O. Schmitt (to whom is due, among other things, the invention of the word "neuroscience"), Jan Boeke (an important Dutch embryologist). In the third row, at the top, from left to right: Viktor Hamburger who invited Levi-Montalcini to join him in Saint Louis in 1947 to carry out experiments on the development of nerve cells, John Piatt, a physicist and writer, Roger Sperry, who would be awarded the Nobel Prize in 1981 for his studies on the split-brain, Jeremy Zachary Young, the discoverer of the giant axon of the squid, on which Hodgkin and Huxley made their famous experiments on nerve conduction. The proceedings of this conference are published in Weiss (1950). Right: The title page of the volume with the proceedings of the conference edited by Weiss and published in 1950 (© Rita Levi-Montalcini).

was most important for him, his ethical stance, had all remained the same.

He never mentioned some vicissitudes and some unfair offences which had made him suffer. His primary attitude was an inclination to forgive those former young students of his who in my opinion had not been loyal to him and had acted aggressively toward him, even though eventually they had become his friends again. From his side, Giuseppe never uttered even a single word of admonishment: "… you know, they are young, one should understand them". Among his human qualities, I consider the ethical ones as the most important. Fortunately, in Moruzzi these were combined with intellectual and cultural qualities. It is for all these reasons that I consider Giuseppe Moruzzi as an example to be followed today. And for you at the school of Parma, I hope that you feel pride because he was educated in this school, at the feet of great teachers. If Italian neurophysiology has indeed achieved an international reputation, we owe that to Giuseppe Moruzzi. It is he, much more than I, who has given Italian neurophysiology a mark of distinction and has carried the name of Italy abroad.

After this personal introduction, indicating my relation with him from the first to the last of our encounters, I would like to describe the figure of Moruzzi from a scientific point of view, despite the fact that I am not as suited to do so as well as his students, his pupils, perhaps even his sons, particularly Paolo who has followed in his father's path (Giovanni is a physicist, perhaps he has not followed the studies of his father

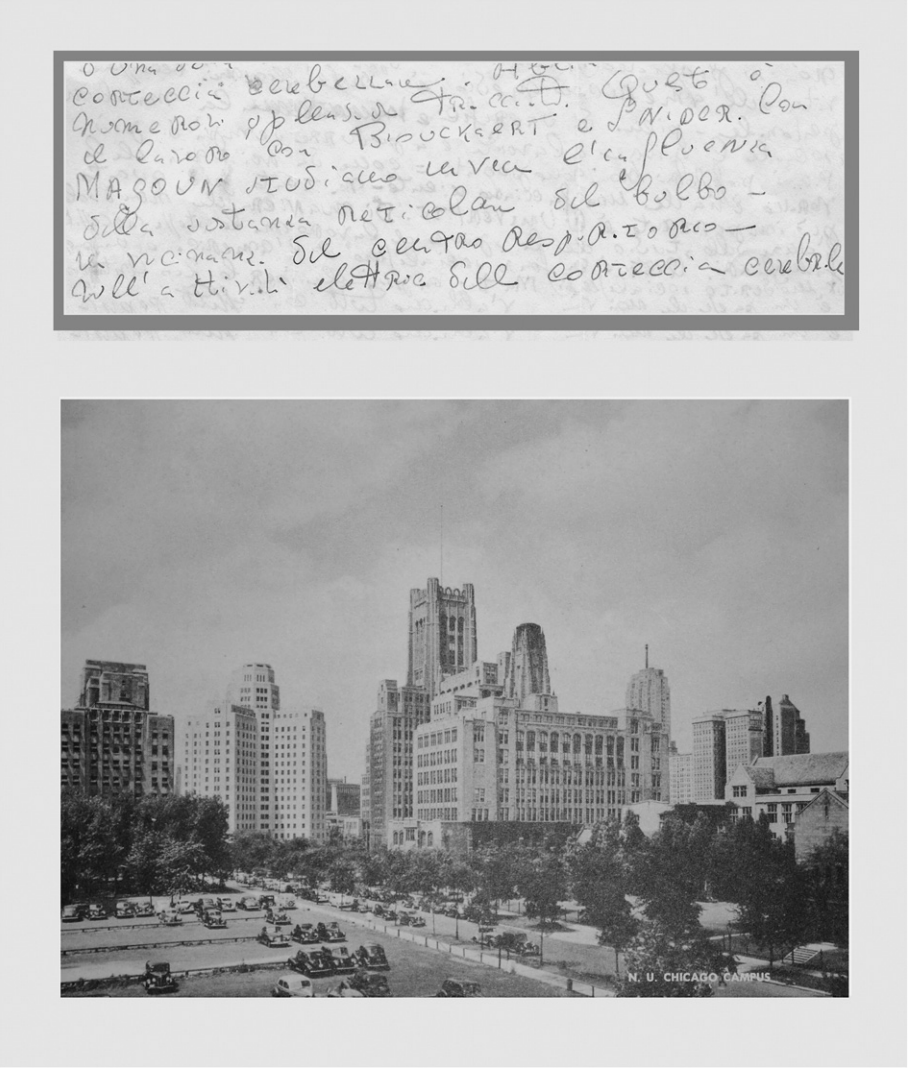

Fig. 5 – Top: A passage of a letter sent by Moruzzi to his parents from Chicago on 14 March 1949 in which he speaks about the research he is carrying out at Northwestern University. After describing the experiments he is doing with John Brookhart and Ray Snider on microelectrode recording of single cells in the cerebellar cortex, he writes: "With Magoun we study instead the influence of the reticular substance in the proximity of the respiratory centre on the electric activity of the cerebral cortex". These investigations were leading to the discovery of the arousal reaction induced by reticular stimulation. Bottom: A picture of the campus at Northwestern University during this period.

with the same intimacy). I wish to outline the research he did, to make clear why we consider him today as a real founding father of research. And if the Nobel Prize was awarded to me and not to him, this was just by chance. It was an error, he deserved it more than I did.[5] As I said, however, neither he nor I have ever given importance to these things. Moruzzi's value has been his enormous creativity, added to his ethical qualities which remain the most important for me.

Even if many of the young people present here may belong to scientific fields other than neurobiology, I believe that it is our duty to describe to them Moruzzi as a man of extraordinary value, and his scientific contributions as an example of what can be done when creativity is combined with an enormous integrity. A life without integrity is worthy of nothing. During my life I have known many Nobel Prize winners.[6] Well, I consider only two or three among them worthy of my unconditioned respect. By itself

[5] The conviction that, together with Horace Magoun, Moruzzi should have been awarded the Nobel Prize was a rather general theme among the international neurophysiological community during the 1960s. It arises from some Levi-Montalcini's writings and particularly from the private letters she wrote to her family in that period (see Levi-Montalcini, 2000).

[6] Levi-Montalcini's relatively low regard for many famous scientists, lacking – in her opinion – sufficiently high ethical, human and cultural qualities, appears in many of her writings (as for instance Levi-Montalcini, 2000). On the other hand, she may show a much higher consideration for more simple people who are endowed with deep human values (see for instance Levi-Montalcini, 1996).

Fig. 6 – Moruzzi in his office at the Physiological Institute of Pisa in 1949 upon his return to Italy. (© Giovanni and Paolo Moruzzi).

the award means nothing, it is the way one behaves during an entire life which counts. In Moruzzi's case one also admires the stoical way in which he faced in the last years of his life a debilitating disease which fortunately did not impact on his intellectual powers. He did it with an incredible stoicism. He never spoke of his disease. We were sometimes together when his physical, but not intellectual, decline was clearly apparent, and yet he never uttered a word about his suffering.

Let us see now what his contributions have been, so that my discourse will not be made of empty words. We consider him a great master in the style of the best Italian schools, but at a higher level than others before him. It is my hope that his formidable school will have followers worthy of him, and there are signs of that.

Moruzzi was educated in Parma at the schools of great teachers, an anatomist, Antonio Pensa, a pupil of Golgi who had received the Nobel Prize in 1906, and Mario Camis, a physiologist (Fig. 8). Moruzzi had a great admiration for Camis, who had worked with some of the great English physiologists, and notably with Barcroft and Sherrington. Camis had devoted himself to the study of the cerebellar system and had passed on to Moruzzi his own enthusiasm for research.[7] From Parma, where he held a position as Camis' assistant, Moruzzi moved in 1937 to Bologna where Camis had been appointed professor of Physiology. Moruzzi happened then to have an opportunity that he considered as one of the greatest chances of his life. Camis, who was acquainted with the greatest international physiologists of the time, contributed to the organisation of a conference which was attended by many important scientists, particularly by Lord Adrian (who had been recently awarded the Nobel Prize) and by others of great fame, like Frédéric Bremer. By meeting the greatest physiologists of his time, Moruzzi could realise that a great research path was open to him, to a mind that was so fervent and agile, and so intensely eager for knowledge.

With Camis' help, and with the support of a Rockefeller fellowship, Moruzzi went for a period of one year to work with Bremer in Belgium (Figs. 9 and 10). From Bremer he was able to learn some basic electrophysiological techniques and particularly the use of electroencephalographic recording to monitor activity of the brain. Electroencephalography was then a recently invented technique which appeared to be of fundamental importance for monitoring the general condition of the brain, in both physiological and pathological conditions. On the sole basis of electric recordings from the surface of the head, one could differentiate the conditions of sleep and waking. Electroencephalography was also of great importance for the diagnosis of pathological states of the brain, and particularly of epilepsy. The technique had been invented in 1929 by a famous German psychiatrist, Hans Berger, and in the 1930s was used with success by Bremer in his experiments.

One of the research topics of Moruzzi in Brussels was the study of some forms of experimental epilepsy, this being the start of his long lasting interest in the convulsive manifestations of the central nervous system (Moruzzi, 1939, 1946). During Moruzzi's period in Brussels, Bremer was working on the brains of animals, usually cats, which had undergone section of the brainstem at different levels. These animals were generally kept alive by artificial respiration. In one of these preparations, dubbed *cerveau isolé*, the section was carried out at a high level of the brainstem, in the midbrain, near the exit of the oculomotor nerve. In this preparation the brain still received two sensory afferences, i.e. the olfactory and visual ones, because the corresponding nerves were still connected to the nervous mass above the section. This notwithstanding, the animal fell in a state with the electroencephalographic characteristics of sleep. It was actually a condition of coma because the animal could not be aroused, even by strong olfactory and visual stimulations.

At that time Bremer was convinced that the comatose state of the *cerveau isolé* preparation was a consequence of the great reduction of the sensory input, in accord with the so-called "deafferentation" theory. In his opinion it was indeed through the action of the overall sensory systems that the brain was activated and kept in a waking state. When, however, the section was carried out at a lower level, i.e. between the medulla and the upper segments of the spinal cord, the preparation, called *encéphale isolé*, underwent an alternation of waking and sleep periods, somewhat similar to the normal condition (Bremer, 1938).

According to Bremer this was due to the greater degree of sensory input which, compared to the *cerveau isolé*, could reach the brain because of the lower level of the brainstem transection. He interpreted the waking state of the brain as due exclusively to ascending inputs arriving to the higher centres through the classical sensory pathways. In his view the waking condition needed the integrity of a significant proportion of the sensory afferences. In the *cerveau isolé* the

[7] As a matter of fact, Moruzzi's interest in the cerebellum predates the encounter with Camis. The cerebellum was indeed the subject of the first article that Moruzzi published at the age of 20, when he was still a student (Moruzzi, 1930).

Fig. 7 – Giuseppe Levi (1872–1965), in a portrait with dedication, donated to Rita Levi-Montalcini (image at the left), and in a photo taken around 1955, near the Institute of Anatomy of Turin with two of his pupils, Rodolfo Amprino and Giovanni Godina. Levi, a great histologist, was the teacher of Rita Levi-Montalcini (and of two other Nobel Prize winners, Salvador Luria and Renato Dulbecco). He was a legendary figure as professor. His singular character, alluded to by Levi-Montalcini in her commemoration of Moruzzi, emerges in a lively way in *Lessico famigliare*, written by his daughter Natalia Levi-Ginzburg, one of the most significant works of *Novecento* literature. As indicated in the dedication, Levi's portrait (shown on the left) was donated to Rita Levi-Montalcini on 26th July 1943. The day before the radio had announced the fall of the fascist government. Levi, who like his pupil had emigrated to Belgium as a consequence of the infamous racial laws adopted by the fascist regime in 1938, had secretly returned to Italy in 1941. With the help of Rita, who had set up a clandestine laboratory in her home, he could continue his research work. The gift of a portrait to the pupil in that particular day was probably a sign of gratitude toward the pupil, in a moment in which there was a prospect of better times for Italy. Things went, however, in a very different ways and, starting from 1943, Italians would suffer the worst consequences of war, particularly because of the military occupation of their country by the Germans. It was in this period that the most cruel episodes of Jewish persecution occurred in Italy, thus making the situation of both Levi and Levi-Montalcini particularly precarious (© Rita Levi-Montalcini for the portrait at the left and Antonio Barasa for the image at the right).

only remaining sensory inputs (i.e. visual and olfactory) were not capable of supporting the waking condition and the animal fell into a condition of continuous and irreversible sleep, i.e. into a state of coma. In the *encéphale isolé*, on the other hand, because of the many sensory afferents supplied by the cranial nerves to their specific cortical areas, the animal alternated between waking and sleep. At that time no connection was known by which sensory inputs could arrive at the brain other than through the specific sensory tracts. As we shall see, Moruzzi gave a different explanation for the general condition of the brain after the transection of the brain stem in the two classical preparations of Bremer. This, however, would happen much later, after 1949, the year in which Moruzzi made his most important contribution to brain physiology in a landmark paper that he published together with the celebrated neurophysiologist, Horace Magoun. Before dealing with this later phase of Moruzzi's work, we need to consider the experiments that he carried out in Cambridge, in collaboration with Lord Adrian, soon after leaving Bremer's laboratory.

As I have already mentioned, when I first met Moruzzi he was still working with Adrian in Cambridge. At the conference in Copenhagen he reported the results of his collaborative work with the celebrated English physiologist. Moruzzi had left Bremer in 1938 at the end of his Rockefeller fellowship and initially had decided to spend a few months in Cambridge using a small amount of money saved from the generous support of the American foundation. Adrian, who immediately saw the benefits of collaborating with the young Italian physiologist, was soon able to secure financial support for him to stay in Cambridge for two years (Fig. 11).

Before considering their very important research, I must say that Moruzzi attributed a great importance to the period spent with Bremer, for both the physiological techniques he had been able to learn and for the intellectual influence of the Belgian scientist. Moruzzi indeed often praised Bremer in his conversations with me and used to say that Bremer had an extraordinary talent for designing experiments.

The research done by Adrian and Moruzzi in the period 1938–1939 in Cambridge was of extreme interest (Adrian and Moruzzi, 1939a,b). The two researchers provided the first recording of the impulsive activity of single cells of the cerebral cortex, the so-called Betz or pyramidal cells of the motor cortex. They showed, moreover, that these cells were continuously active, even in the resting state and in the absence of any overt motor activity. Adrian and Moruzzi recorded from these cells at the level of the

Fig. 8 – Moruzzi's teacher, Mario Camis (1878–1946), in a portrait with a dedication sent to his pupil from Manila in 1939. Camis, of Jewish origin, eventually embraced the Catholic religion and entered the Order of Dominicans. Expelled from the University as a consequence of the infamous racial laws promulgated by the fascists in 1938, he went first as a missionary to Manila and then, during the Nazi occupation of Italy, founded a shelter. He died in Italy. On Camis, see Moruzzi, 1949 and Berlucchi, 2005. (© Giovanni and Paolo Moruzzi).

fibres they emit and which form the pyramidal tract at the base of the encephalon, in the region of the medulla. They found that in the resting state these fibres discharge at a low rate of a few impulses per second, and this discharge is not able to elicit any visible movement; it is – as we say – subthreshold for inducing contractions. When, however, an excitatory drug (such as strychnine) was locally applied to the motor cortex, the discharge rate became very high, up to 1000 impulses per second. This frenzied activity led to convulsions and epileptic movements.[8]

For the first time the capacity of cortical cells to send a continuous train of impulses was established, even in the resting state of the animal, showing that the brain was never in a condition of absolute quiescence. This activity was modulated by physiological or experimental influences which eventually led to behaviours such as the movement of limbs. These movements could be of a convulsive type when the cortex was put in a state of extreme activation by local application of excitatory drugs. Moreover, this work demonstrated for the first time that the basic electrical activity of cortical cells was made of short impulses, completely indistinguishable from the signals discharged by peripheral nerve cells and even by muscles. These impulses appeared to be the general signals used by the nerve cells to code and transmit the information on which our movements, sensation, and even our overall mental activity depend.

These were the first studies that made Moruzzi's name known in the scientific world, and when I first met him he was enthusiastic about this work. On that tragic day in Copenhagen, he was very much concerned about the difficulty he would have in continuing this work because of the impending war. He decided however to return to Italy where he was afterwards enrolled as a medical officer in the army (Fig. 12). Thus, our paths separated almost as soon as we met. I returned to Italy, too, but perhaps some of you know my history because it is written in a book (Levi-Montalcini, 1987). After serving in the army as a doctor, at the end of the war Moruzzi resumed his academic career and eventually went to the U.S.A. By chance I also went to the U.S.A., to Saint Louis, and therefore I was not far from Chicago where he was working.

This was a very famous period in Moruzzi's scientific life, yielding results which have opened an immense field of research and have led many to ask why he was not awarded the Nobel Prize.

Until then Moruzzi's endeavour had been that of carrying out (in collaboration with great teachers) important studies on various experimental preparations: the *cerveau isolé* or *encéphale isolé* with Bremer, the study of cortical cells with Adrian. These investigations were really important, as I have already mentioned above, and had made Moruzzi famous in the scientific world. So famous that I was really struck when I first met him, saying to myself how astonishing was that the celebrated Moruzzi was such a very young man.

Nonetheless, that work did not have the impact on neurophysiology that was achieved with the research carried out in the period 1948–1949, and that Moruzzi would pursue until the end of his life. The impact of these subsequent researches is still strong in contemporary neurophysiology. I will mention them briefly because they are really important and even non-specialists cannot ignore them. At those times practically nothing was known about the mechanism whereby the cerebellum affected the activity of the neocortical regions of the brain. Magoun, who I met in that period and I would see many times afterwards, had made some important discoveries concerning cerebellar influence on the low levels of central nervous system. He had shown that certain zones of the paleocerebellum (that is the phylogenetically old portion of the cerebellum), had an important inhibitory influence on the spinal cord. Magoun had discovered that the activity of the motor cells in the spinal cord that are under the control of cortical motor neurons, is actually modulated by an input coming from the paleocerebellum, through the fastigial nucleus. In other words, he had discovered an action mediated through a descending pathway, belonging to the so-called reticular formation of the brainstem.

Working on this system Moruzzi and Magoun made a very important and totally new discovery (see Figs. 13, 14 and 15).

[8] Moruzzi himself remembered the excitement of his work with Adrian in some of his writings, and particularly in his unpublished *Recollections* which is now a part of a recent book dedicated to him (Meulders et al., 2010 pp. 41-121).

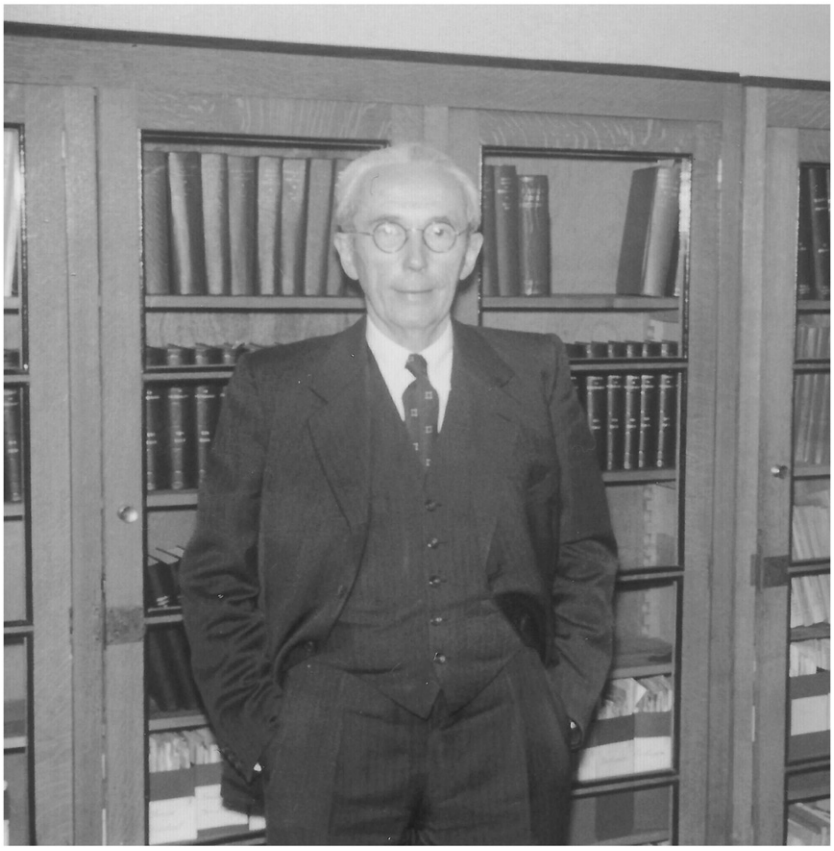

Fig. 9 – Frédéric Bremer (1892–1982) in 1959 in his office at the University of Brussels. (© Giovanni and Paolo Moruzzi).

This was the discovery of the important role of ascending paths existing in the reticular formation, i.e. of an "ascending reticular system" as it was called by the two researchers. In an attempt to ascertain the mechanisms of the inhibitory action of the cerebellum on the spinal cord and motor cortex, Moruzzi and Magoun found, somewhat by chance, that the electrical

Fig. 10 – Frédéric Bremer with John Brookhart (1913–1995) on the occasion of the first congress of the "International Brain Research Organization" (I.B.R.O.) held in Pisa in 1961. Brookhart was one of the many distinguished physiologists with whom Moruzzi collaborated. (© Giovanni and Paolo Moruzzi).

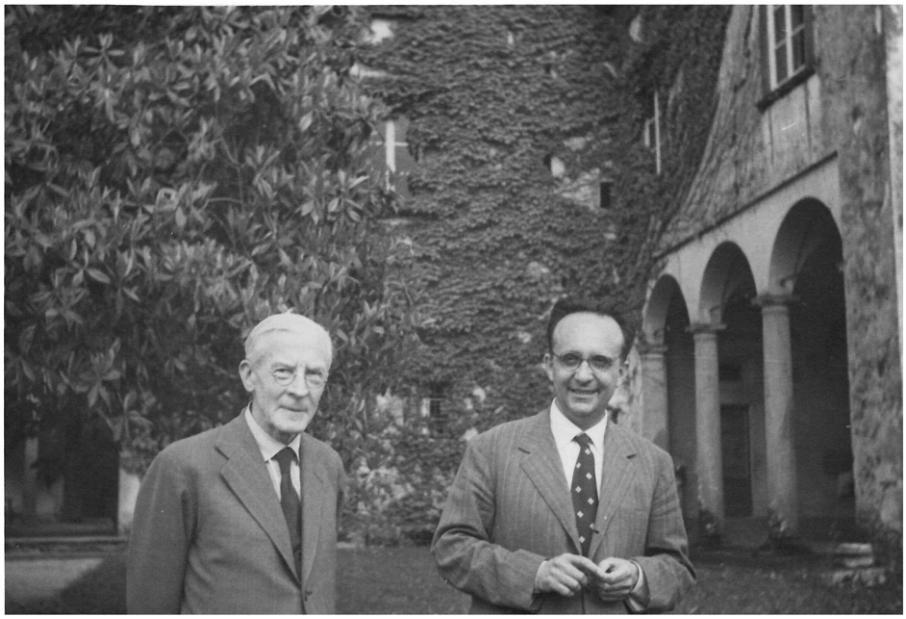

Fig. 11 – Edgar Douglas Adrian (1889–1977) and Giuseppe Moruzzi in 1954, during a visit at Villa Torrigiani, a splendid aristocratic mansion near Lucca. Moruzzi, who had a great taste for art and history, often accompanied his foreign guests on visits to the monuments and artistic sites near Pisa. The friendship between Adrian and Moruzzi continued for a long time after the Cambridge period and, in 1952, Moruzzi translated into Italian Adrian's famous book on perception (Adrian, 1947) and on his later years he wrote two articles about his former teacher (Moruzzi, 1980, 1982) (© Giovanni and Paolo Moruzzi).

Fig. 12 – A portrait of Giuseppe Moruzzi as a medical officer during the war, in 1942. (© Giovanni and Paolo Moruzzi).

stimulation of the reticular formation leads to a generalised arousal reaction in the cortex. This would prove to be the basis for the control of the sleep–waking cycle in the brain and would provide a rationale for the previous experiments of Bremer on the *cerveau isolé* and *encephale isolé* preparation.

As mentioned above, the Belgian physiologist attributed the arousal action of sensory influence in his preparation mainly to the classic sensory nervous pathways carrying sensory signals to specific zone of the brain. After Moruzzi and Magoun's work, it turned out that the main role was played by the reticular formation. From the time of Cajal, this relatively diffuse part of the brainstem was called reticular because of the reticular aspect of its cells and fibres. Until the work of Moruzzi and Magoun, its role and physiological importance were almost totally ignored. Afterwards, the reticular formation occupied the foreground of neurophysiological investigations. The preparation *cerveau isolé*, was not, as Bremer had supposed, in a state of continuous comatose sleep because of the paucity of sensory input, but because it was deprived of the action of a great part of the "ascending reticular system".

I remember well Moruzzi and Magoun's enthusiasm when their paper was published in 1949. I remember also their enthusiasm when they showed me the results when the paper was still in press. They showed me how, through the electrical stimulation of the reticular system, the arousal reaction was produced in the cat cortex; that is, the waking condition. If that formation is excluded from the brain because of the high level of the transection, the animal remains in state of sleep, irrespective of how it is stimulated. We know now that in general anaesthesia, we have an inactivation of the ascending reticular system, fortunately a temporary one.

Fig. 13 – Giuseppe Moruzzi while seated at a stone table in the family house at Bombodolo near Parma in August 1948, shortly before leaving for Chicago. From his childhood, and until the last years of his life, he spent his summer holidays at this place, and there, according to his *Recollections*, he wrote many of his scientific papers. The discovery of the activating action induced in the brain cortex by the stimulation of the reticular system was made by Moruzzi and Magoun in March 1949, and was published in the same year in the first issue of a new journal, *Electroencephalography and Clinical Neurophysiology*. (© Giovanni and Paolo Moruzzi).

In subsequent experiments conducted in Pisa, Moruzzi and his students were able to localise different centres within the reticular formation, with opposite effects on the sleep–waking condition. Some of them led to arousal, others, localised at a lower level of the brainstem, were endowed with a sleep-inducing action (see Batini et al., 1959 and Moruzzi, 1963).

Upon his return to Italy, Moruzzi devoted himself to these studies, and directed his attention to the significance of his discoveries to the general physiology of the brain, and the control possibly exerted by the reticular system on vegetative nervous function. He was able to attract to his institute in Pisa many brilliant students and he founded a research centre that would soon become famous throughout the world. In the 1960s he also created, alongside the main physiological institute of the University, a neurophysiological laboratory funded by the Italian National Research Council (C.N.R.). This institution was also situated in Via San Zeno, an old street in Pisa which became a pole of attraction for many scholars and researchers coming from all parts of the world.

Moruzzi made his experimental studies in an extremely refined way which, in my opinion, stands as a model for young people entering the field of research. Among his papers, I particularly recommend his Harvey Lecture, and other general lectures on the sleep and waking cycle, and also the two

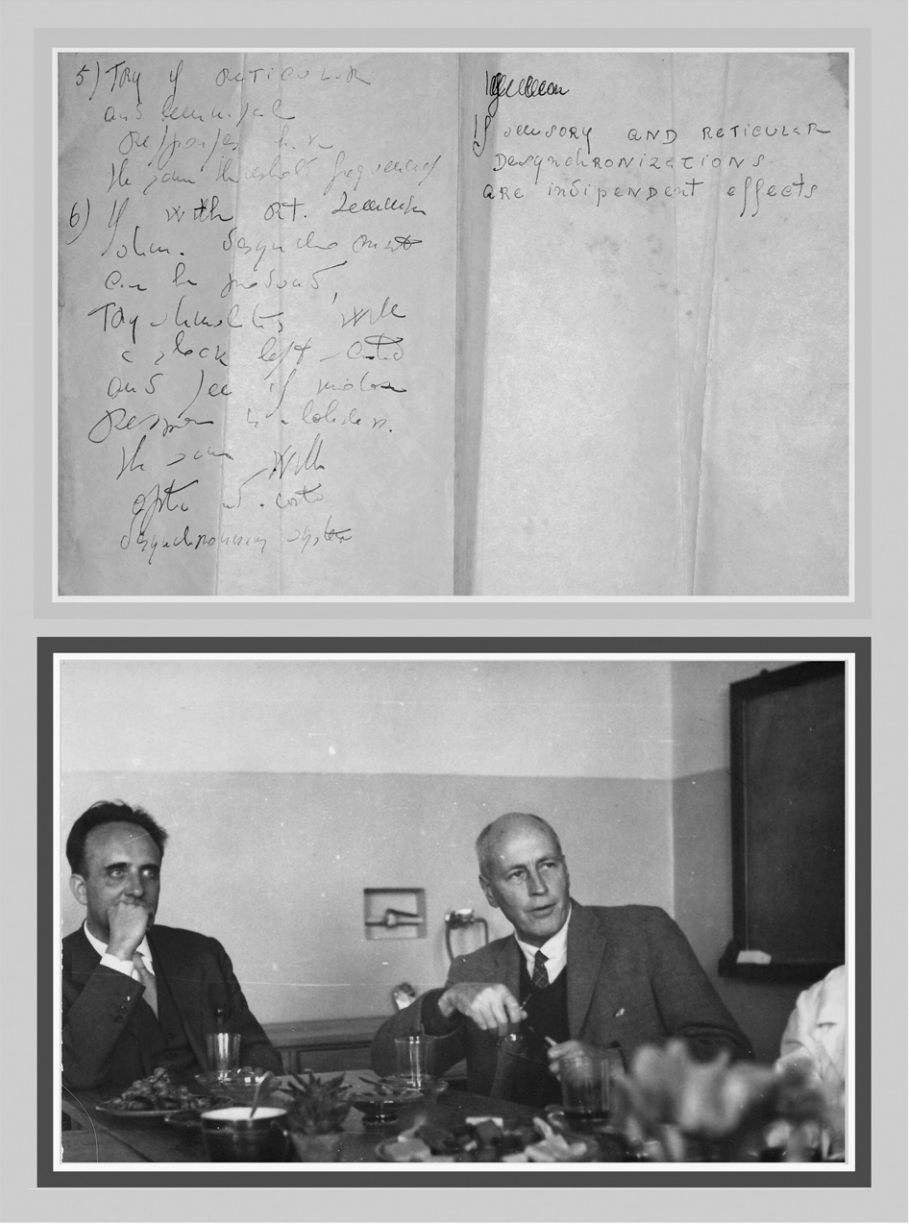

Fig. 14 – Top: The back page of Moruzzi's handwritten undated loose sheet of paper indicated as "Plan of the experiments in Chicago" with a list of various experiments to be performed on the reticular substance at the Northwestern University. The last statement says: "Sensory and reticular desynchronizations are independent effects", one of the important conclusions of Moruzzi and Magoun's work. Bottom: Moruzzi with Magoun during a break at the "International Colloquium of Electroencephalography of Higher Nervous Activity" held at Moscow in October 1958. (© Giovanni and Paolo Moruzzi).

splendid volumes of his recently published treatise of physiology (Moruzzi, 1963, 1971, 1972, 1975, 1978, 1981, 1986).

Reading what Moruzzi has written helps us to appreciate the importance of being capable of perceiving the experiment in its complexity. He was never tied to the concept of the "small experiment", as now often happens with young researchers, who know everything about, let's say, molecular engineering, or of other experimental techniques, but lose the global vision, the importance of what they are looking for with respect to the totality of the organism. If there is research that we can call a classic, both with regard to the way it was carried out and to its aims, this was certainly Moruzzi's research on the ascending reticular system. It concerned the function of this system, its role in the sleep–waking cycle, on the emotional system, on the hypothalamus and on a variety of other systems.

Step by step an immense amount of data was accumulated, concerning the reciprocal influence of the reticular system with the other systems of the body. In his research Moruzzi also used the most refined microelectrode techniques, which allowed him and his collaborators to investigate the electrical activity of single cells. He investigated the modulation of the activity of these cells in a variety of physiological and experimental conditions. He studied many fields, and in all of them he left important contributions concerning both the physiology and the pathology

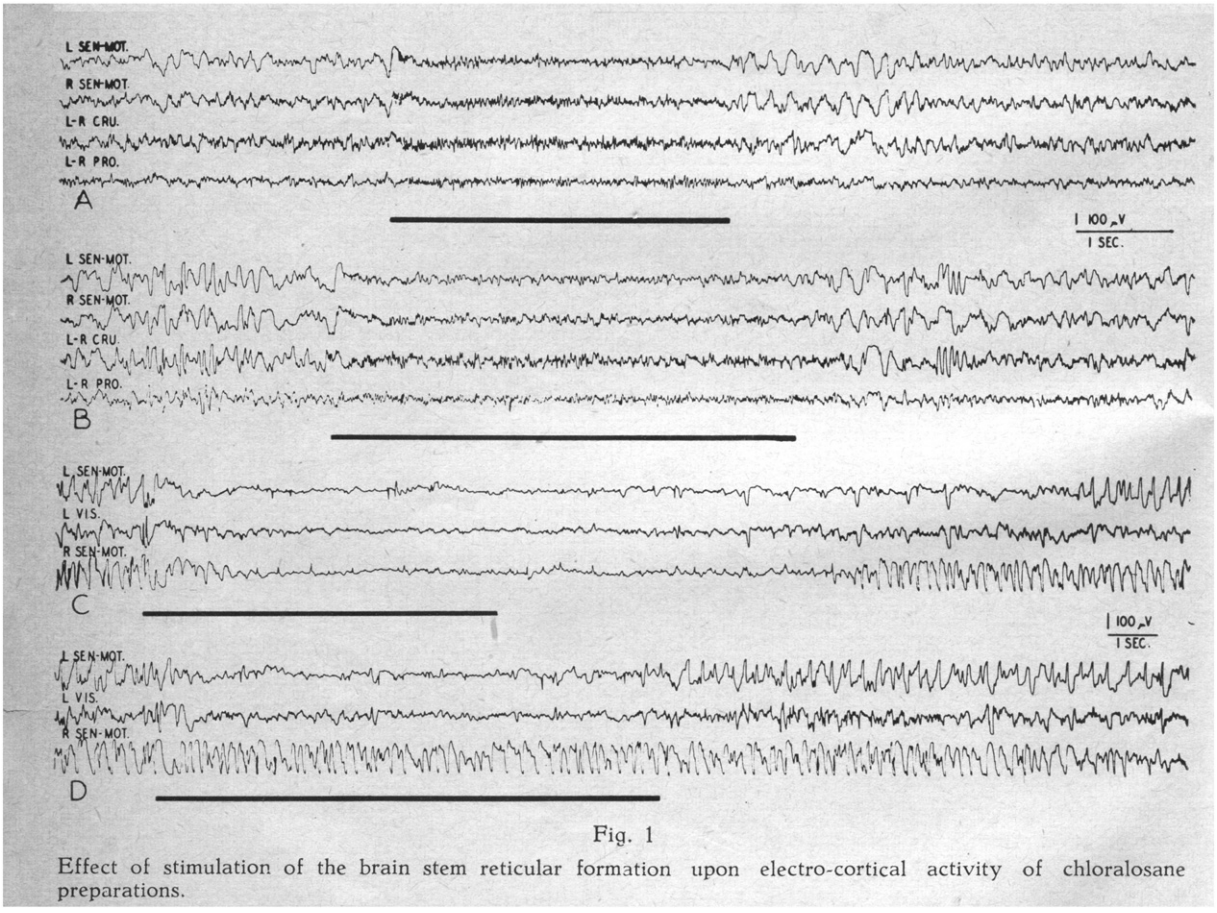

Fig. 1

Effect of stimulation of the brain stem reticular formation upon electro-cortical activity of chloralosane preparations.

Fig. 15 – A figure from Moruzzi and Magoun's (1949) article showing the electroencephalographic arousal reaction induced by the electrical stimulation of the reticular formation in the cat.

of the nervous system. I mention here, among his many texts, the fundamental volume on the physiology and pathology of the cerebellum that he published in 1958, in collaboration with Robert Dow (Dow and Moruzzi, 1958). It is a volume that I have studied intensively and almost learned by heart. The interest in the cerebellum was a long standing one for Moruzzi. It had started since his studentship in Parma with Pensa, and was a continuation of an important Italian tradition. Indeed, between the late nineteenth and the early twentieth century, two Italian neurophysiologists, Luigi Luciani and Gilberto Rossi have added fundamentally to the study of this important part of the central nervous system.[9]

I do not believe that I should continue talking to a non-specialist audience about the other fields that were opened by Moruzzi's work, I will only say that what remains is the memory of a formidable scientific personality, the memory of an exceptional man. If I am here today, and if I consider the tribute that has been given to me, as more properly due to him, this is because people like him can recreate, in the young, the faith in research and knowledge and show the way research should be conducted.

Moruzzi is the perfect example of that, from the human and the cultural points of view – he had a very strong humanistic understanding in addition to the rest – and from the point of view of the scientific capacity. To that he added an enormous generosity. If an important school has emerged around him, which comprises so many people who cannot be named here, this is due to these outstanding qualities. Moruzzi gave to the others the same motivation he had in his life. It is this curiosity, this intensity of research that also allowed him to face with great stoicism the difficulties of his life. A person engaged in life as he was, does not fear anything. I am pretty sure, even though we never discussed it together, that he was not much interested in his physical condition. Until the end of his life, he had only one desire: to work with the maximum of intensity, the maximum of honesty, and by helping others.

If Italy is known around the world in the context of biology, and especially in neurophysiology, that is all due to a son of this land, to Giuseppe Moruzzi.

[9] Luigi Luciani (1840–1919) was an Italian scientist who made important contributions in different fields of physiology including the study of the cerebellum and the brain cortex. He became particularly famous for his treatise on human physiology which underwent numerous editions in Italy, and was translated into various languages. Moruzzi, who was strongly interested in the history of science, wrote a historical note on Luciani which was published in 1955 (Moruzzi, 1955) in a trilingual edition (English, French, and German). Gilberto Rossi (1877–1960) was an eminent biochemist and physiologist. He was first to discover the facilitatory influence of cerebellar stimulation on the movements driven by the motor cortex. After his retirement from the University teaching, Rossi devoted himself to literature and published an autobiography, *Mezzo contadino*, in 1952. He was greatly admired by Moruzzi who wrote an obituary note on him (see Moruzzi, 1960).

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