The neurological school of Prof. Cornelio Fazio (1950-2010)

From the lecture delivered by Prof. Cesare Fieschi, MD, PhD, Professor Emeritus of Neurology, University of Rome, winner of the XXII Ottorino Rossi Award. New Series “The Founders of Neurology” - 21 June 2011

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I first met Prof. Fazio in Genoa, in 1956, the year in which I graduated and he took up his position as professor and chairman of the Neurological Clinic there. Ten years earlier, he had published an article entitled “Studies on focal cerebral vascular lesions”, which showed his interest in this disease. However, neither that article, nor the neurology textbooks published for at least another fifteen years, were able to shed any light on why cerebral infarcts can occur when postmortem studies subsequently show many arteries to be open. Arterial spasm and blood steal phenomena were among the weak explanations advanced.

In Genoa, Prof. Fazio had met Prof. Carlo Loeb, who gave him valuable help for many years, but the school’s specific role in and commitment to this field actually began in 1959, the year in which I specialised in neuropsychiatry, as the discipline was then known. With the words “Fieschi, you will be responsible for stroke”, Prof. Fazio gave me the task of looking after this area, entrusting me with a six-bed room in his Neurological Clinic in Via de Toni where patients with acute stroke were hospitalised.

At that point, the merits of Prof. Fazio, which at the time I failed to see as such (I felt hopeless with regard to what I could really study in our patients and do for them, apart from take good care of them), were closely related to three key developments: the establishment of the stroke centre, or stroke unit; the establishment of a neuroradiological unit in his department; and the establishment of bimonthly post-mortem brain dissection sessions in the Neurology Clinic.

His was a truly visionary initiative, the only one of its kind in Italy. However, still disheartened by the very little that could be done at that time to study this disease and help patients, I soon went to work in the United States, at the National Institutes of Health in Bethesda, specifically at the Laboratory of Cerebral Metabolism. For years, with many interruptions, I worked on cerebral blood flow and metabolism. Some very useful scientific data started to appear, such as those that introduced the concept of the therapeutic window. Contrary to what physiological studies had previously shown, the brain was not irreparably damaged within minutes of focal cerebral ischaemia; rather, the damage occurred gradually, over the space of several hours.

In the meantime, the school of Prof. Fazio, who was supported by Prof. Loeb and Prof. Giberti, had developed in two directions: neurophysiology and psychopharmacology. Therefore, the late 1960s saw me occupied, once again, with the task I had been given in 1959. This period culminated in 1969 with the publication of angiographic studies done with the young Dr Luigi Bozzao (later Professor of Neuroradiology), who had been assigned to me as a graduate trainee. It was certainly a bold undertaking to investigate cerebral circulation from the acute phase of ischaemic stroke using carotid angiography by direct injection of the contrast medium in the ICA in the neck, and measurements of cerebral blood flow that, in the meantime, I had imported from the United States. What we observed and published in our article “Transient embolic occlusion of the middle cerebral and internal carotid arteries” (1) represented an absolute novelty (see figure), confirmed moreover by postmortem study of brains, which were sent to us intact, after fixation, from the Institute of Pathology.

Carotid angiography, frontal view. The image on the left was taken six hours after a right ischaemic stroke; the exam was repeated five days later (left image) (ref. 1)
Indeed, we found that many arteries that had appeared occluded by emboli or thrombi on the first angiographic study were actually open, as we had already seen them to be on follow-up angiography. This was the first international study to show this unexpected event.

At that time, patients were not required to provide declarations of consent, and this allowed us to complete our research. Many years have now gone by since our observations, which, also repeated in the United States, led to the hypothesis that it might be possible—as it had already been shown to be in myocardial ischaemia (through the formidable Italian GISSI study, coordinated by the Mario Negri Institute)–to develop an effective reperfusion treatment, necessarily performed within the first few hours of the event. However, streptokinase, effective for the heart, proved risky in stroke. Indeed, in an American study it was found to cause cerebral haemorrhage. Therefore, we had to wait for the advent of recombinant tissue plasminogen activator (rt-PA) whose efficacy was demonstrated by two international studies, one European (called ECASS) and the other American (NINDS), both published in 1993. Whereas in our European study the drug was administered within a maximum of five hours of symptom onset, the American study limited the therapeutic window to three hours. Therefore, only the latter produced statistically significant results. This study led to registration of the drug by the Food and Drug Administration (FDA) as early as 1994. All of us, like our American counterparts, observed numerous cases of patients “recovering” while still lying on the CT scan bed—patients who had received the intravenous thrombolytic therapy as soon as the diagnosis was confirmed. James C. Grotta, at the 1992 congress of the American Heart Stroke Council, coined the expression “spectacularly shrinking deficit” to describe this phenomenon, and this is exactly what it was.

While the school in Genoa continued under the leadership of Prof. Gandolfo, Prof. Fazio’s school had, in 1969, moved to Rome and it is opportune at this point to recall his many collaborators whose efforts allowed so many studies to be conducted: Lenz, Carolei, Argentino, Rasura, Toni, and Sacchetti. They deserve to be mentioned by name because many studies, both experimental and clinical, were not possible without them: these include the repetition of many angiographic study within six hours, and an international multicentre study of treatment of acute stroke completed, with another drug, within five hours. This latter study is important because Italy’s first “stroke unit”, at the Policlinico Umberto I in Rome, was opened precisely in order to perform this research. Initially it was based in Prof. Fazio’s Neurological Clinic; subsequently, in 1999, it was moved to the hospital’s Emergency Department in order to speed up the diagnosis and thrombolytic treatment. In 2002 we opened a second stroke unit at the Ospedale Sant’Andrea. Furthermore, still in Rome, other colleagues, drawing on our experience, opened units at other hospitals (Policlinico Gemelli, Policlinico di Tor Vergata, Ospedale San Camillo).

Although, by this time, Prof. Fazio had ceased his university activities, he always continued to follow closely the studies of his school.

I wish to end with a few final remarks, beginning on a negative note. The registration of rt-PA in Europe was not authorised until a full nine years after its registration in America, providing an indication of the cultural slowness we confronted in that period.

On a more positive note, however, many colleagues in other centres were nevertheless able to perform the treatment in the context of clinical trials. Indeed, European studies in this field—the SITS-MOST and ECASS 3 trials among others—ensured that this remained a priority area, in Europe and in Italy. Many stroke units were created (even though too slowly in my view). Today they number more than a hundred, but they are not evenly distributed and, in particular, do not cover the regions south of Rome. I nevertheless wish to applaud Lombardy, the region in which I am speaking today, which, in this regard, has achieved greater growth and organisation than Lazio, where everything began.

Finally, I wish to say a word about what I expect from the future and in this regard draw your attention to the title of a recent article published in the Journal of the Neurological Sciences: “Large numbers of stroke physicians should be used to treat large numbers of stroke patients with IV rt-PA” (2). Herein lies, in my view, the best solution for the health care system and thus for patients too: what we need is not many more stroke units (crucial centres especially in the training of specialists and in the continuation of research endeavours), but rather an adequate number of “stroke neurologists”, qualified specialists working in emergency departments to increase the number of acute stroke patients who recover or improve. Specific training of these specialist neurologists will help our discipline to go on playing a key role in health care, and will also benefit the National Health System, given that patients who are well treated in the acute phase will cost less (shorter hospitalisations, less severe residual deficits). Such an endeavour may generate advantages: both human and economic benefits for the patients themselves, for their families and for society at large. This is, indeed, documented by the Italian Health Ministry’s CCM project, begun by me and completed by Prof. Inzitari with the collaboration of the Italian centre for social investment studies, Censis. This study would certainly have met with Prof. Cornelio Fazio’s approval, as he was always concerned with the social aspects of medicine. I dedicate my lecture to him.

References

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Cornelio Fazio (1910-1997)

Cornelio Fazio was one of the most important Italian neurologists of the twentieth century. Born in Garessio, on 30 March 1910, Fazio was the son of an important politician of the liberal tradition, who was opposed to the rising Fascism. He graduated in medicine at the University of Turin in 1935 where he worked at the Institute of Anatomy headed by the famous morphologist Giuseppe Levi and was a colleague of Renato Dulbecco, Rita Levi Montalcini and Salvador Luria. In 1937 Fazio joined Lionello de Lisi at the University of Genoa where he began his scientific career in the neurological field. In 1938 he developed a method for studying the vascular system and demonstrated the vascular difference between the white and grey matter of the spinal cord (subsequently named the Pickworth-Fazio method). Meanwhile he actively participated in the Italian movement against Fascism as a member of the political group “Giustizia e Liberta” (Justice and Freedom) and, during the dark years of 1943-1945, risked being arrested and condemned to death. After the Second World War he continued his clinical work at the neurological clinic of Genoa under the direction of his master Lionello de Lisi. During this period he conducted important research on vascular diseases of the encephalon, on the relationship between cerebral infarction and heart diseases, on the malformation of the circle of Willis and on the reduction of mortality from brain vascular disease as a consequence of food restriction during the war. When de Lisi retired in 1955, Fazio succeeded him to the chair of neurology at the University of Genoa and began to form a school of neurology, which quickly rose to prominence in Italy. In 1969 he moved to the chair of neurology at the University of Rome where he where he stayed until he retired, becoming Professor Emeritus in 1985. His scientific life was marked by important investigations both in neurology and psychiatry. Among his important achievements are those obtained with his pupils Alessandro Agnoli and Cesare Fieschi on the usefulness of blood flow measurements by means of radioactive isotopes to investigate cerebral vascular diseases. He was also an advocate of neurorehabilitation and one of the first to understand the revolutionary importance, for psychiatry, of antidepressant drugs for the treatment of dysthymia. The life of Cornelio Fazio was always full of pupils and collaborators. Among the important neurologists who were directly influenced by him as a master, both in Genoa and in Rome, we can remember: Carlo Loeb (his successor at the chair of neurology in Genoa), Cesare Fieschi, Alessandro Agnoli, Mario Manfredi, Orso Bugiani, Emilio Favale, Gianluigi Lenzi, Massimiliano Prencipe, Franco Giberti, Luigi Bozzaio and Adolfo Brusa. Cornelio Fazio died in Rome on 11 March, 1997.