LAUDATIO ON PROFESSOR GIANCARLO CARLI: ON OCCASION OF HIS RETIREMENT FROM ACADEMIC DUTIES

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It is my pleasure to pay tribute to Professor Giancarlo Carli, in view of his creative and multifaceted contributions to the neurosciences for more than 50 years. Essentially: all of Carli's work was never *l'art pour l'art* just to produce sophisticated science concepts, but in all his fields the ultimate aim in his experimental and clinical research was to help suffering human patients.

In 1959, at the age of 21, Carli entered the Physiology Laboratory of Siena University as a medical student, and was immediately set alight by science—obviously this was a key event in determining his subsequent life, a career as a neurophysiologist. His first publication was published in *Science* (Carli et al., 1963), reporting on central pathways controlling the recently discovered rapid eye movement (REM) sleep. Seeing his publication in one of the most prestigious scientific journals must have been a tremendous reward for the young author and certainly reinforced his motivation to carry on in the neurosciences.

An interlude followed in the USA from 1969 to 1971 when Carli spent a training fellowship on the psychophysics and neurophysiology of skin mechanosensation at Johns Hopkins University in Baltimore, in the group of Vernon Mountcastle at the Department of Physiology. Carli and LaMotte studied the threshold sensation of the hand in humans and monkeys via the frequency of vibratory stimuli, showing virtually the same quantitative stimulation-response characteristics in both species (Mountcastle et al., 1972). This work became fundamental to the contributions of Meissner's and Pacinian corpuscles and their afferent nerve fibres in low versus high frequency sensation, and is referred to in some textbooks on the somatosensory system.

From 1965 Carli continued his sleep research at the famous Institute of Professor Giuseppe Moruzzi at Pisa University, with Ottavio Pompeiano as his supervisor. Moruzzi's research focus was on the non-cognitive functions of the nervous system, such as the sleep–wake cycle, the mechanisms and control of electroencephalography (EEG), the origin of emotions and motivations, and levels of consciousness, which he attributed to the ascending reticular activating system (ARAS) in the brainstem reticular formation and hypothalamus. This novel concept had been introduced through a seminal publication by Moruzzi and Magoun in 1949.

Working in the intellectual environment of a worldwide famous institute obviously was a favourable condition for Carli to become involved in several research projects, as is reflected in a total of 17 publications that appeared in 1966 and 1967, in 12 of these Carli was the first

author. One of the novel results was that afferent somatosensory information transmission was blocked during phases of REM sleep, and that the mechanism of presynaptic inhibition was responsible for sensory control during sleep states (Carli et al., 1966). At this time our group in Heidelberg was studying the functional role of spinal presynaptic inhibition in tactile sensations, and we noticed with great interest the report from Pisa strongly supporting the physiological importance of this novel inhibitory mechanism in relation to sleep states. For his early contributions to the understanding of sleep mechanisms Carli was awarded a Pioneer on Sleep Studies by the Sleep Research Society in 2003.

In 1967 Carli was invited by Professor Moruzzi to set up a new laboratory on hypnosis in animals. The label of hypnosis in animals was used for a state of tonic immobility that was induced, for example, in rabbits by laying them on their back. In this abnormal position animals remained immobile for minutes, with all mono- and polysynaptic motor and righting reflexes totally suppressed. Animals even showed neither convulsive movements during evoked brain seizures documented in the EEG nor escape reactions to painful stimuli—thus motor behaviour was totally suppressed during this state of immobility.

Carli alluded to the potential survival value of this immobility reaction, an aspect studied many years later (e.g. Fanselow & Helmstetter, 1988) as freezing reaction. David Livingstone (1872) reported an attack by a lion during an expedition in Africa: 'I saw the lion just in the act of springing upon me, and we both came to the ground together. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake by a cat. The shake annihilated fear, and allowed no sense of horror in looking around at the beast. The peculiar state is probably produced in all animals killed by carnivores.' Today this behavioural state is considered as an innate protective reaction in some extremely life threatening situations (e.g. an encounter with a predator), and this behaviour is therefore also termed a death feigning reaction (see Lefebvre, this issue). Pharmacological studies in Carli's group revealed that endogenous opioids were not involved in tonic immobility.

From 1978 onwards intensive study with Francesca Farabollini was aimed at identifying the endocrinological changes associated with animal hypnosis (reviewed by Farabollini, this issue). They found that corticosterone and testosterone levels essentially remained stable during the state of hypnotic immobility, suggesting a kind of functional endocrine buffer working to maintain endocrine balance, in spite of the presence of a stressful situation. This neuroendocrine stability differentiates the hypnotic state from the alternative emergency reaction as originally described by Cannon (1915), and is associated with huge activation of the hypothalamic-pituitary-adrenal axis paralleled by autonomic and motor defence reactions.

The condition and accompanying electrocortical phenomena of tonic immobility in animals suggest some similarity to catalepsy in humans. Carli and Lefebvre (reviewed by Lefebvre, this issue) pointed to another protective behaviour observed during childbirth in monkeys where the mother remains silent in spite of great pain during parturition: crying as a normal reaction to pain would attract predators and thus endanger the lives of the mother and newborn. In 1969 Carli received an award by the American Institute of Hypnosis for his early studies on animal hypnosis.

Work on animal hypnosis continued until 1984 and was followed in 1989 up until now by a study of physiological factors associated with hypnotic susceptibility in humans, a project which began with the thesis of Enrica Santarcangelo (Santarcangelo et al., 1989) and is still continued by her, in cooperation with Carli. Human subjects were classified by their high ver-

sus low capability to enter into a state of hypnosis. These studies revealed that hypnotizability in humans was associated with differences, for example, in spinal motor reflexes, postural and locomotor control, the preference for specific imagery modalities, the embodiment of imagery, and also in the cardiovascular effects of nociceptive stimulation (Santarcangelo et al., 2008). While classically the understanding and theory of hypnosis in humans had been largely based on psychodynamic theories, the studies by Carli and Santarcangelo helped disclose the importance of neuro- and psychophysiological factors as causative or modulatory mechanisms. Their findings imply suggestions for new therapeutic approaches using hypnosis as a medical tool.

Interestingly, James Braid, a founder of hypnosis in the 19th century, conceived that his novel therapy was based on psychological phenomena rooted in multiple physiological processes. Prior to Braid, Franz Anton Mesmer in the 18th century had suggested that magnetic forces originated from the doctor and were transmitted to the patient to induce healing. Thus Mesmer was convinced of a physiological process involved in the transmission of therapeutic effects from the doctor to patient, although his tenet of 'animal magnetism' was declared a misconception by the Societé Royale in Paris. With approaches such as those of Carli and Santarcangelo, physiological processes are returning to the basis of hypnotherapy in the 21st century, and will hopefully contribute to the understanding of some of the underlying mechanisms. For advancing the concepts of hypnosis Carli was awarded honorary membership of the Italian Medical Association for the Study of Hypnosis.

In 1988 pain research appeared in Carli's bibliography. Obviously the focus on pain emerged from his previous projects, which had included the interference of pain stimuli on sleep and hypnosis in animals. Now the formalin test was applied to induce pain behaviour in animals in a controlled way, initiating a long period of pain studies on animals. In addition, Carli's research projects on human pain recently became of great significance in the prevention and treatment of pain in patients, as detailed below.

One of the innovative animal studies by Carli, together with Francesca Farabollini, was on the effect of prolonged pain on social behaviour and hierarchy in a group of rabbits housed in a natural environment (Farabollini et al., 1988). Formalin pain was induced in the dominant male. In spite of the dramatic decrease in motor and social activities due to the pain, the social ranking order of the animals was not eliminated, although the amount of aggressive actions was much reduced in the dominant animal, but not in the other group members. In conclusion, at least for the initial two days, persistent pain was not able to affect the pre-existing territorial situation and rank orders within the group; flight behaviour was maintained in subordinates, while the social activity of the whole colony sharply decreased.

One of their projects, in collaboration with Anne Gabriel at Maastricht University, studied the effect of environmental social and physical enrichment in rats, using subcutaneous formalin to induce a pain status of several hours in duration (Gabriel et al., 2010). The duration of mechanical allodynia was maximal in rats housed in a restricted environment and was reduced to a lesser extent in rats housed in an enriched environment (physical and/or social). In particular it was shown that increasing the physical activity of the animals resulted in a concomitantly larger reduction of the duration of mechanical allodynia, anticipating applications for physical and mild sporting activities in humans to prevent and treat musculo-skeletal pain.

In 1988 Anna Maria Aloisi became involved in Carli's animal pain research, culminating in two comprehensive review articles on complex pain behaviour and its neuroendocrinological

background following tonic pain (Carli & Aloisi, 1993; Aloisi & Carli, 1996). From this cooperation, Aloisi's own project on the sexual differences in pain mechanisms and behaviour emerged.

In the 1990s Carli, as a neurophysiologist, had a leading role in two remarkable clinical projects: the post-surgery care of patients without using opioid analgesic drugs and the study of patients with fibromyalgia syndrome (FMS) to reinforce the experience of well-being and countering pain.

The standard post-operative care of patients recovering from major surgery (i.e. thoracotomy) usually includes analgesic treatment with opioids. Carli learned from the Bologna University Department of Surgery that patients were offered post-surgery recovery with no use of opioid analgesics. Instead, patients received intensive social support, including visits by their family, to create a psychological setting in which the patient's expectation was strengthened as a means for the self-control of pain. These principles are in line with factors determining the placebo effect, which were studied by Benedetti's group at the University of Turin (Lui et al., 2010). This work revealed that the level and persistence of placebo analgesia is associated with the patient's expectations and learning from previous experience of pain and pain control. Thus Carli, in cooperation with Valeria Bachiocco from the Bologna Clinic, assessed patients with questionnaires to predict individual levels of perceived pain and their potential to stay without opioid analgesics. The Ethical Committee of the International Association for the Study of Pain (IASP) recommended publication of the manuscript which was submitted to the journal *Pain*, as a case of a distinctive ethnic feature in handling pain. However, the editor of *Pain*, disregarding the *votum* of the Committee, rejected the manuscript because of ethical concerns, claiming that patients were inadequately treated for their pain. As a consequence, as chairman of the Ethical Committee of IASP, I stepped back as an expression of my protest against the editor's verdict. Fortunately the work by Bachiocco and Carli was published in other distinguished pain journals (e.g. Bachiocco et al., 1990), and is considered a forerunner in acknowledging ethnic solutions for the care of patients in pain.

In 2002, a project on patients suffering from FMS was started in cooperation with Giovanni Biasi from the Rheumatology Clinic of Siena University. Carli introduced the Italian version of the Multidimensional Pain Scale (MPS), a pain questionnaire developed at Columbia University in New York where Carli had been a visiting professor in 1993. The MPS included the dimension of well-being in the profile of pain subjects. Surprisingly, many FMS patients self-rated high levels of well-being, in spite of their multi-locular pain that typically did not sufficiently respond to analgesic medication or other therapy. Thus Carli and his group (Anna Lisa Suman and Alexa Huber) started to consider well-being as a separate psychological dimension partially independent of the suffering of pain. They devised a multidisciplinary treatment programme based on cognitive behavioural therapy and aerobic physical training. Surprisingly, and against the predictions of many who had devised treatments for FMS previously, the results showed reduction of pain to tolerable levels (Suman et al., 2009). At the same time, analysis of blood monocytes showed increased expression of glucocorticoid receptors, suggesting improved function of the hypothalamic-pituitary-adrenal axis in counteracting pain mechanisms and experience. The treatment programme induced a persistent change in the self-concept and physical activity behaviour in most of the FMS patients involved in the programme.

Thus, the neurosciences owe an impressive contribution from Giancarlo Carli's life work (www.giancarlocarli.com). The synopsis I have personally gained when preparing this laudation shows to me his great motivation and ability to unveil some of the secrets at the interface

between the subconscious and cognitive spheres of the brain and behaviour. His continued curiosity was obviously seeded 50 years ago as a beginner in neurophysiology and then shaped by the Moruzzi school of neuroscience. I have known Giancarlo personally for some 40 years, as a cultivated gentleman of classical education with a good sense of humour and, most importantly, as a reliable friend—thank you, Giancarlo!

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