Review Article

Robert Naquet (1923-2005): The Scientific Odyssey of a French Gentleman

Carlos Cepeda¹, Tatsuya Tanaka², Jean-Marie Stutzmann³, and Henri Korn⁴

¹Mental Retardation Research Center, University of California, Los Angeles, USA.

²Department of Neurosurgery, Asahikawa Medical College, Asahikawa, Japan

³Sanofi Aventis, Vitry sur Seine, France

⁴Institut Pasteur, Paris, France

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Abstract

Fig. 1. Dr. Robert Naquet in his office of Gif-sur-Yvette in 1980. Photograph taken by T. Tanaka.

This biographical note pays a small tribute to Robert Naquet, one of the pillars of French epileptology together with Henri Gastaut, his mentor. It can be said that the Marseilles school of epilepsy left an indelible mark in the neurological sciences and that there is no epileptologist, in France and abroad, who was not influenced by the teachings of these two gentlemen. It is practically impossible to separate the scientific achievements of Robert Naquet from his multiple facets as a humanist, artist, and teacher. His warm personality and legendary modesty may serve as an example for future generations of neuroscientists.

Send correspondence to: Carlos Cepeda, Ph.D.
MRRC, Semel Neuroscience Institute, room 58-258, UCLA School of Medicine, 760 Westwood Plaza, Los Angeles CA, 90024
Tel: (310) 206-0861 Fax: (310) 206-5060 Email: ccepeda@mednet.ucla.edu

« *Le conceptuel, ce n'est pas mon rayon, je fais de la recherche parce que ça m'amuse. Je suis curieux, je sais regarder, mais c'est tout* » Robert Naquet (online reference A)

« Conceptual thinking is not my thing. I do research because it amuses me. I am curious, I know how to look, but that's all »

Robert Naquet was to French experimental epilepsy what Henri Gastaut, his mentor and friend, was to French clinical epilepsy research. Both men have reached the same scientific stature and their legacy will forever be remembered as another glorious period of French neurology. It can be said that the Marseilles school of epilepsy has left an indelible mark and that there is no epileptologist, in France and many other countries, who was not influenced by or did not benefit from the teachings of these two gentlemen. In this article we want to pay a small tribute to Robert Naquet, our friend and teacher, who departed quietly the night of December 7, 2005 at the age of 82 years. His passing offers an opportunity to those who had the privilege of knowing this incomparable man, to reflect on the meaning of being a scientist. Above all because R. Naquet, « Boby » to his close friends, showed them the path of scientific research, first by his example and second by showing them that science, though difficult at times, offers unlimited satisfaction provided we ask the right questions. Because he was a medical doctor, he emphasized that these questions, whenever possible, should lead to improving our lives.

R. Naquet used to say that he lived the

“grande époque” of neurophysiology. A period filled with discoveries but also grand illusions, because it was then possible to believe, with some ingenuity, that just by looking at the waves of an electroencephalogram (EEG) it would be possible to unravel the general principles governing brain function. Raised amidst the great tradition by the pioneers of neurophysiology, he collaborated with giants such as G. Moruzzi, H. Magoun, H. Jasper, and, of course, his mentor H. Gastaut. Very few scientists could presume thereof but he never bragged, as one of his traits was a legendary modesty.

R. Naquet was born in Avignon on April 26, 1923. He always preserved an unhidden love for Provence (even though he could very well be taken for a native Parisian). He loved the landscapes, the flowers, the sea, and he saw them with the regard of a painter, his favorite pass time. Passivity and indecision bothered him to the extreme, and until the end of his life he remained active. He had a profound knowledge of people and was a natural psychologist able to listen and always being ready to give advice to anyone who requested it. How could one forget his favorite advice to the young investigators as well as to his close friends, “be prudent”. His passing leaves a great vacuum. We lost not only an original scientist but also an incomparable friend whom we could always rely upon for support.

In this biographical sketch, a compendium of his 50 years in neurobiology, some of his principal scientific contributions to neuroscience will be evoked. The number of his collaborators and pupils was so great that it

would be practically impossible to mention all the people who participated in his research. We ask to be excused for any omission, but if we learned something from our irreplaceable mentor and friend, it is that humility is a great virtue and also that silence does not mean forgetfulness.

The origins of his interest for neurophysiology

The interest of R. Naquet for the brain was manifested at a very young age. When still a young student at the Faculty of Medicine in Marseille participating in the Resistance, he always had a book of anatomy of the nervous system (online reference A). Jean-Didier Vincent, his successor as Director of the Laboratory of Neurophysiology in Gif-sur-Yvette (online reference B), tells the story of how R. Naquet met Captain Charles Lenormand in the Maquis. He was the group commander and also a professor of physiology at La Sorbonne, where he had been a pupil of Louis Lapicque. Becoming inseparable, both used to talk about the future at the foot of Mont Rose, where some pockets of enemy troops encroached. “What interests me the most”, said R. Naquet, “is the anatomy of the nervous system”. “You would be better off if you did neurophysiology”, retorted Lenormand, “it is the science of the future”. At that very moment, a shell exploded in a neighboring field and hit a white horse that reared back and jumped in the air. This vision was a sign of destiny that defined his scientific career.

R. Naquet met Henri Gastaut around 1948, during his internship. H. Gastaut was going to

open a neurophysiology laboratory and invited R. Naquet to work with him. He made his debut in science by serving as guinea pig for Gastaut, who was studying the effects of intermittent light stimulation on the EEG. Another premonitory sign, but then R. Naquet was far from realizing that twenty years later he was going to discover a type of reflex epilepsy induced by light that was going to be associated with his name forever.

His first and last passion, epilepsy

To replicate in animals the manifestations of human epilepsy was the challenge that R. Naquet and his colleagues in Marseille faced at the beginning of the 1950s. Working in Gastaut’s laboratory, and under the direction of Georges Morin (Dean of the Faculty of Medicine), R. Naquet in association with R. Vigouroux (future Mayor of Marseille), A. Roger (née Beaumanoir), J. Corriol, and collaborators demonstrated that electrical stimulation of the amygdala through chronically implanted electrodes (Gastaut et al., 1952a; Morin et al., 1952) or injections of alumina cream in the same region (Gastaut et al., 1952b) were able to induce psychomotor seizures. These observations revealed the multiplicity of projections of amygdaloid post-discharges, as well as their origin in the rhinencephalon (Gastaut et al., 1953). These studies were the subject of his thesis in 1953 (Naquet, 1953) and they served as the basis for the discovery, a few years later, of the kindling phenomenon by F. Alonso De Florida and J. M. Rodríguez-Delgado (1958) and G. V. Goddard (1967). These early successes

strongly stimulated the spirit of this young investigator. Throughout his long scientific career, R. Naquet discovered, created or improved numerous epilepsy models. He also influenced other investigators to be more sensible to epileptic phenomena and taught them how to interpret paroxysmal activity on the EEG, myoclonic manifestations in the animal, as well as the anatomic lesions associated with epilepsy.

Beneficiary of a fellowship from the Rockefeller Foundation, R. Naquet continued his training at the University of Pisa (1952-1953) with G. Moruzzi, then at the University of California Los Angeles (1953-1954) with H. Magoun, the co-discoverers of the ascending reticular activating system. Those were the years during which plenty of studies were oriented towards investigating the mechanisms of wakefulness and sleep. These investigations, along with those on epilepsy, received great impetus, thanks to the utilization of the EEG which was able to reveal the state of cortical excitability. The EEG still remains an essential diagnostic tool in epilepsy and a reliable indicator of wake and sleep states. With G. Moruzzi and A. Mollica, he examined the effects of cerebellar stimulation on reticular activity (Mollica et al., 1953). R. Naquet worked with H. Magoun and Ellen Eva King (his later collaborator in Marseille) on afferent transmission in the thalamus and its modulation by central mechanisms and barbiturates (King et al., 1957). The variations in this transmission allowed them to conclude that, contrary to prevalent belief, the thalamus is

not a reliable relay of somatic inputs. R. Naquet frequently reminisced on the profound influence exerted on him by Magoun, who taught him the way of reasoning (online reference A). Still in Long Beach, he collaborated with his close friends J. P. Segundo and P. Buser in the study of the activating effects of cortical stimulation in monkeys (Segundo et al., 1955).

R. Naquet was always able to associate his experimental research with his clinical work and never lost the practical dimension or the possible applicability of the data obtained in the laboratory. With the Gastauts, J. E. Paillas, G. Salamon, A. Fernández-Guardiola, M. Fisher-Williams, J. Bert, F. Morrell, and others, he studied the effects of photic stimulation on human cortical excitability (Naquet et al., 1959; Naquet et al., 1960), the EEG correlates of hematomas (Paillas & Naquet, 1950), tumors (Paillas et al., 1953), anoxia (Gastaut et al., 1958), as well as the conditioning of synchronous discharges in cats and rabbits (Morrell et al., 1957).

In 1965 R. Naquet with his American friends Eva and Keith Killam, then on sabbatical leave from Stanford University, discovered genetic photosensitive epilepsy in the Senegalese baboon *Papio papio* (Killam et al., 1966a, 1966b, 1967). This observation soon attracted numerous French and foreign investigators, all aspiring to elucidate the causes of this photosensitivity. First in Marseille, then at the Laboratory of Neurophysiology (LPN) in Gif-sur-Yvette, where he became director in 1972, C. Ménini, G. Vuillon-Cacciuttolo, M.

Poncet, D. Riche (who established an atlas of the *Papio papio*), F. Bostem, J. Catier, S. Dimov, J. Wada, T. Tanaka, S. Brailowsky, C. Silva-Barrat, J. Velluti, and many others contributed to unraveling the mechanisms underlying photosensitivity (Brailowsky et al., 1975; Carlier et al., 1973; Catier et al., 1975; Fischer-Williams et al., 1968; Fukuda et al., 1988; Menini et al., 1968, 1970; Morrell et al., 1969; Naquet et al., 1975; Naquet & Wada, 1992; Silva-Barrat et al., 1986; Silva-Comte et al., 1982).

Pharmaceutical trials were soon to follow, hoping to one day be able to treat human epilepsy. It was thus that investigators like B. Meldrum, A. Valin, J. M. Stutzmann and many others tested new drugs on the photosensitivity of baboons (Meldrum et al., 1974; 1979a; 1979b; Naquet & Meldrum, 1986). When J. Rossier arrived at the LPN, the race to find an endogenous ligand of benzodiazepine receptors was underway. The carbolines were good candidates and, by examining the effects of β -carbolines on the photosensitivity of *Papio*, C. Cepeda and J. Rossier discovered the proconvulsive properties of this endogenous ligand (Cepeda et al., 1981). Since then, the study of the carbolines occupied the LPN for many years (Chavoix et al., 1991; Kaijima et al., 1984).

The multiple aspects of photosensitivity in *Papio papio* preoccupied R. Naquet throughout his life. In a last work on the effects of videogames in photosensitive subjects, he and his collaborators gave specific recommendations to prevent seizures, such as the use of

television screens of 100 instead of 50 Hz (Badinand-Hubert et al., 1998). But his studies of photosensitivity did not prevent R. Naquet from discovering or improving other epilepsy models, in particular temporal lobe epilepsy. The discovery of kindling promoted intensive research at the LPN by G. Le Gal la Salle, T. Tanaka, H. Lange, V. Leviel, and E. Cavalheiro (Le Gal la Salle et al., 1981; Leviel & Naquet, 1977). Also, when glutamate analogs such as kainic acid started to be utilized to induce selective lesions of neuronal somata, Y. Ben-Ari, E. Tremblay, Le Gal la Salle, C. Ménini and others used it to induce amygdaloid seizures (Ben-Ari et al., 1981; Menini et al., 1980). The deep knowledge of R. Naquet concerning temporal lobe lesions was essential to demonstrate distant lesions induced by seizures. Once again, his previous work on the antiepileptic virtues of Valium (Gastaut et al., 1965) made it possible to restrict the extent of those lesions (Ben-Ari et al., 1978).

A few years later, S. Brailowsky joined R. Naquet's team at Gif. He was interested in gamma-aminobutyric acid (GABA) and, using mini-pumps implanted in the cerebral cortex of *Papio*, he studied the effects of this amino acid on seizure activity. In collaboration with C. Ménini, C. Silva-Barrat, and others, he observed that the epileptic discharges induced by photic stimulation were blocked by GABA. This was to be expected. However, after the pumps were removed, they realized that the baboons manifested epileptic discharges and even seizures at the very site of perfusion. This is how the GABA withdrawal

syndrome was discovered (Brailowsky et al., 1987; 1988; Le Gal la Salle et al., 1988). Since then it became a useful model to study the physiopathology of focal seizures.

The vast body of evidence gathered from the *Papio* model of epilepsy suggested that the cerebral cortex, in particular the fronto-rolandic area, played a primordial role in the genesis of photic seizures, and that the regions in the brain stem were involved only secondarily. But the centrencephalic theory of generalized epilepsy, promulgated by W. Penfield and H. Jasper, was still present in R. Naquet's mind. Could the brain stem play a role, particularly if we consider the existence of myoclonia without cortical manifestations, which appear to originate in the brain stem (Naquet & Valin, 2000; Valin et al., 1981)?

R. Naquet had been very interested in the work of the embryologist Nicole Le Douarin. He understood early the advantages of the method used to create neural chimeras in birds that she had developed since 1969, as it permitted the transfer from an individual to another from the same or even another species, of a genetically determined trait or behavior. He thus had the idea to transfer the genetic epilepsy of a chicken (Fayoumi) to another healthy one, in order to discover the cerebral regions involved in the triggering of photic or auditory seizures, which closely resembled those in humans. With M. A. Teillet, C. Batini (who remained a faithful collaborator and accompanied him through the difficult path of his emeritus status in France), and others, he studied the effects of different grafts in the prosencephalic, mesencephalic or rhomben-

cephalic regions between the embryos of two chickens. These works reinstated the place of the mesencephalic region of the brain stem as a possible generator of generalized seizures (Batini et al., 1996; Fadlallah et al., 1995; Teillet et al., 1991). However, R. Naquet wanted to go further in the exploration of the causes of genetic reflex epilepsy. He tried to determine the gene or genes responsible for this syndrome in the chicken. To achieve this goal he mobilized and motivated two teams of geneticists, those of M. Tixier-Boichard and F. Pitel. This was a far-reaching work that required plenty of enthusiasm and energy. The determination of the monogenetic nature of this type of epilepsy followed by localization of the gene were achieved just before his passing. In common agreement, all collaborators of Naquet decided to pursue and even expand this investigation so close to his heart.

Throughout his life, R. Naquet tried to define more precisely the nature of the epilepsies. Are they better characterized by the paroxysmal discharges on the EEG or by their clinical manifestations? But, some discharges have no clinical manifestation and conversely some myoclonia are not epileptic. Naquet's contributions will serve undoubtedly to provide a more precise definition of this disconcerting syndrome.

Sleep and extreme conditions

The mechanisms of sleep and wakefulness always elicited R. Naquet's interest, all the more so as he had been a pupil of Magoun and Moruzzi and also to distance himself from Gastaut. His contributions to this field were

different, but not less important, than those of his great friend M. Jouvet.

At the beginning of the 1960s, in collaboration with M. Dénavit-Saubié, J. Lanoir and D. Albe-Fessard (from the Institut Marey), R. Naquet studied the role of diencephalic structures in supporting sleep and wakefulness. The traditional idea that the thalamus played a critical role in the triggering of sleep, based on the fact that spindles occurring at the beginning of sleep are generated by this structure, was debunked by the observation that a cat without a thalamus is still capable of sleeping (Naquet et al., 1965). On the other hand, with the use of thermodes that allowed local and transitory cooling of deep brain structures, R. Naquet, M. Dénavit-Saubié and D. Albe-Fessard demonstrated the existence of a region at the level of the dorsal subthalamus involved in the maintenance of wakefulness (Naquet et al., 1966a). An important implication of this observation was that the reticular formation is not the sole region capable of supporting wakefulness.

The nature of sleep–epilepsy relationships occupied an important place in the investigations of R. Naquet. The specificity of sleep organization in cats and various primates, including *Papio papio*, were the subject of numerous publications in association with collaborators such as J. Bert, J. Engel, E. Balzamo, G. Vuillon-Cacciutolo, and others (Naquet et al., 1966b). The effects of epileptic manifestations of kindling or limbic status epilepticus on sleep organization were also studied with T. Tanaka and C. Cepeda (Cepeda et al., 1982a; Tanaka & Naquet,

1975, 1976). These studies evidenced the sleep perturbations induced by epilepsy.

In a field related to those previously mentioned but still little explored, the pioneering work of R. Naquet on the effects of high pressure on cerebral activity left an indelible mark on his career. These studies were performed at the Experimental Hyperbaric Center (COMEX) in Marseille. In collaboration with R. W. Brauer, A. Gosset, P. Fructus, and particularly J. C. Rostain, he characterized a neurological syndrome in individuals exposed to high pressures (Brauer et al., 1969; Naquet et al., 1984; Rostain et al., 1983). He also demonstrated that high pressures decrease paradoxical sleep (Rostain et al., 1997) and facilitate epileptic seizures in monkeys (Rostain et al., 1971). These results led to better working conditions for divers, as well as the prevention of neurological syndromes in extreme conditions.

For his clinical and scientific competence, R. Naquet became a respected voice in the Delegation for Research and Technique (DRET) of the Army. Also, he contributed to important research on human physiology in space, another subject very close to his heart. He participated very actively in the scientific council of the National Space Agency (CNES) and directed efforts for the acquisition of financial support for research; he also followed enthusiastically the spatial missions of French cosmonauts.

Cerebral imaging

The advent of new techniques to visualize

cerebral functions greatly attracted the attention of R. Naquet. He was one of the first to recognize the importance of non-invasive methods for brain studies such as positron emission tomography (PET), while the vast majority of neuroscientists then considered it a method that is costly, complicated, and not amenable to provide new information. In contrast, R. Naquet understood immediately the implications of the possibility to study, in primates and humans, *in vivo* metabolic activity and neurotransmission in normal and pathological conditions. The Hospital Service Frédéric Joliot from the CEA (Center for Atomic Energy, in Orsay) was located near Gif, which allowed him to perform experiments using PET, in collaboration with D. Comar, M. Mazière, J.C. Baron, and others. He was one of the first to study glucose metabolism during epileptic seizures, as well as the displacement and kinetics of benzodiazepines in the brain of baboons (Cepeda et al., 1982b; Comar et al., 1979; 1981; Mazière et al., 1985). Numerous investigators from the CEA and Gif, such as P. Hantraye, E. Brouillet, H. Fukuda, M. Kunimoto participated in these studies (Hantraye et al., 1986).

With D. Ancri and collaborators at the Hospital of La Pitié-Salpêtrière, he studied the modifications of cerebral blood flow during the onset of generalized seizures induced by light in *Papio papio* baboons, examining their correlations and demonstrating that cerebral blood flow does not follow passively the changes in blood pressure (Ancri et al., 1979). It was thus natural that after J. Horowitz passed away, R. Naquet was asked to become

President of the GIP (Public Interest Group) Cycéron at Caen, the second center for PET imaging created in France.

Robert Naquet and the Life Sciences Department in the CNRS

In 1980 R. Monier, the new Director of the Department of Life Sciences and General Director of the CNRS (National Center for Scientific Research) decided that, due to its scientific importance, this department required the presence of two adjunct Directors. This decision led to the nomination of N. Le Douarin and R. Naquet.

R. Monier and R. Naquet had met for the first time at the campus of the CNRS in Marseille. Recognizing his insufficiencies in the field of neurosciences and of physiology in general, R. Monier persuaded the President and General Director as well as the Ministry of Higher Education and Research to nominate R. Naquet, whose scientific competence and human qualities he had appreciated. This is how a multitude of intricate problems were solved thanks to the intelligence, benevolence, and aptitude for negotiation of R. Naquet, whose support allowed a number of laboratories to be created, equipped, and developed. There too his exceptional qualities found ways to benefit the main organization of public research in France. He remained in this post until 1991. Many of these tasks were aided by the diligence and incomparable efficiency of his loyal secretary at the LPN, Annick Omnès.

Ethics and other areas of interest

Two virtues can be applied to R. Naquet; kindness and honesty. He was always ready to intercede in support of medical research, which he considered essential for human well-being (Naquet, 1993). Indeed, he was an infallible defender of animal research, for which he paid a heavy tribute, and not always found the institutional support he needed. It is thus not surprising that he dedicated great amounts of time to the Ethics Committees (online reference C).

It was to honor the memory of his wife,

Michelle, who passed away before him, that led him to the gargantuan task of organizing the correspondence of his father-in-law André Maurois, one of the great French luminaries of his time. R. Naquet knew well the historic value of his correspondence and donated a great deal to the Institute of France. Dominique Bona shared the same passion, and it is based on those letters that the book « Il n'y a qu'un amour » (There is only one love) was published.

He was a Correspondent Member of the French Academy of Sciences, section of Hu-

Fig. 2. This photograph of a smiling R. Naquet was taken at the beautiful Rishiri Island in Hokkaido, Japan, just before his participation in the 40th Annual Meeting of the Japanese Society of Clinical Neurophysiology held in Asahikawa City, 2003. Photograph taken by Tatsuya Tanaka.

man Biology and Medical Sciences, which has yet to understand how much it owed, and still owes, to Naquet's dazzling scientific career; at the Academy, he participated regularly in the studies of the Committee of Space Research. A very modest man, R. Naquet was nonetheless happy to having been named Commandeur of the French Legion of Honor. He also enjoyed greatly when, in 2003, his pupils and friends organized a very successful Colloque in Marseille to celebrate his 80th birthday, and 50 years in science (Fig. 3). For his multiple and important contributions to neuroscience,

for his mentorship and advice to various generations of scientists and, above all, for being a constant example of kindness and honesty, R. Naquet deserves an important place in the Pantheon of epileptology.

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Fig. 3. Dr. Naquet with his friends and students during the Colloquium to celebrate his 80th birthday held in Marseille, 2003. Photograph taken by H. Tsuda.

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